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ORIGINAL CONTRIBUTIONS

Volume 20 September, 1953 Number 9

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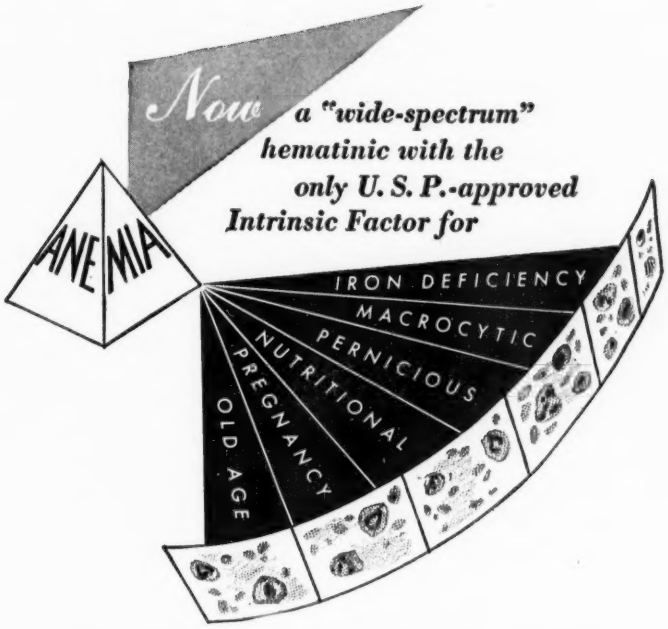

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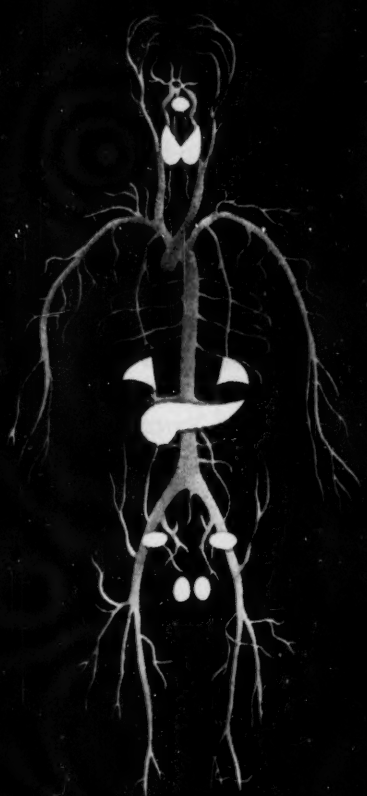

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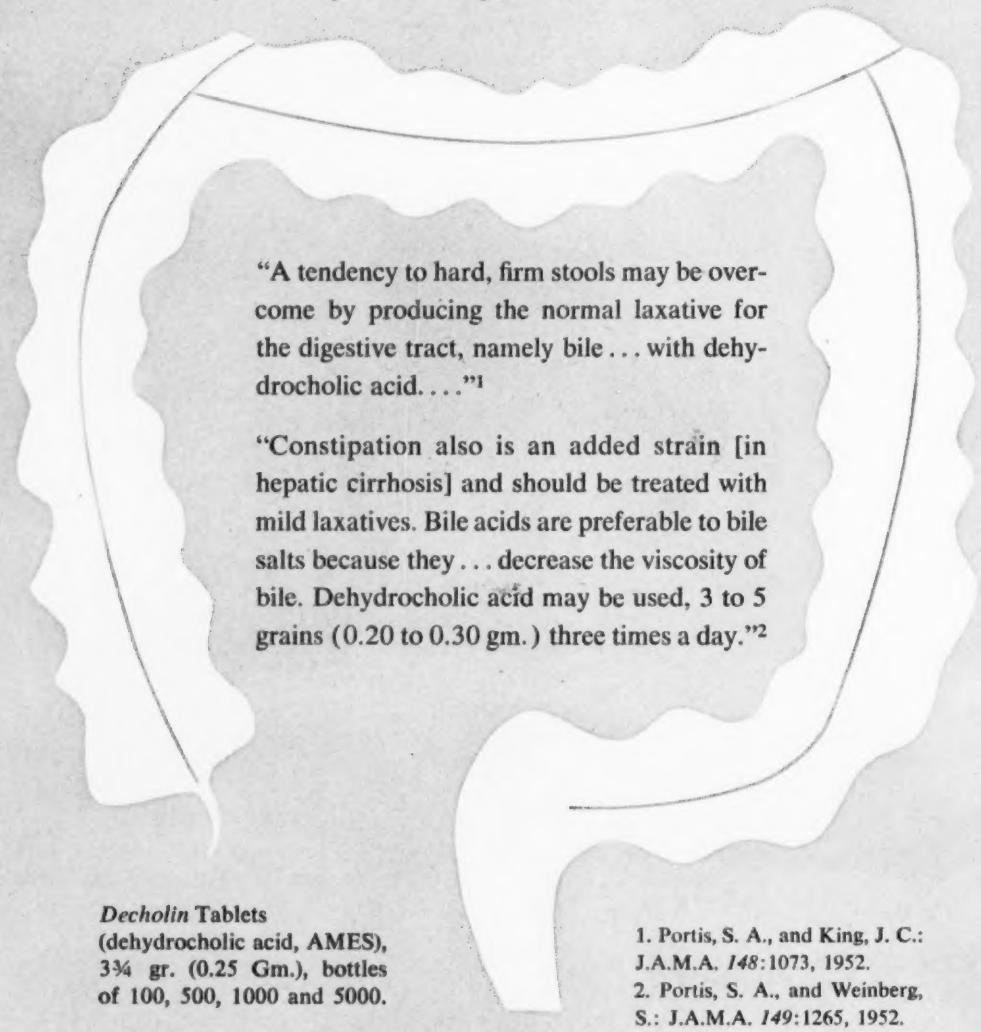

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1. Portis, S. A., and King, J. C.: J.A.M.A. *148*:1073, 1952.
2. Portis, S. A., and Weinberg, S.: J.A.M.A. *149*:1265, 1952.

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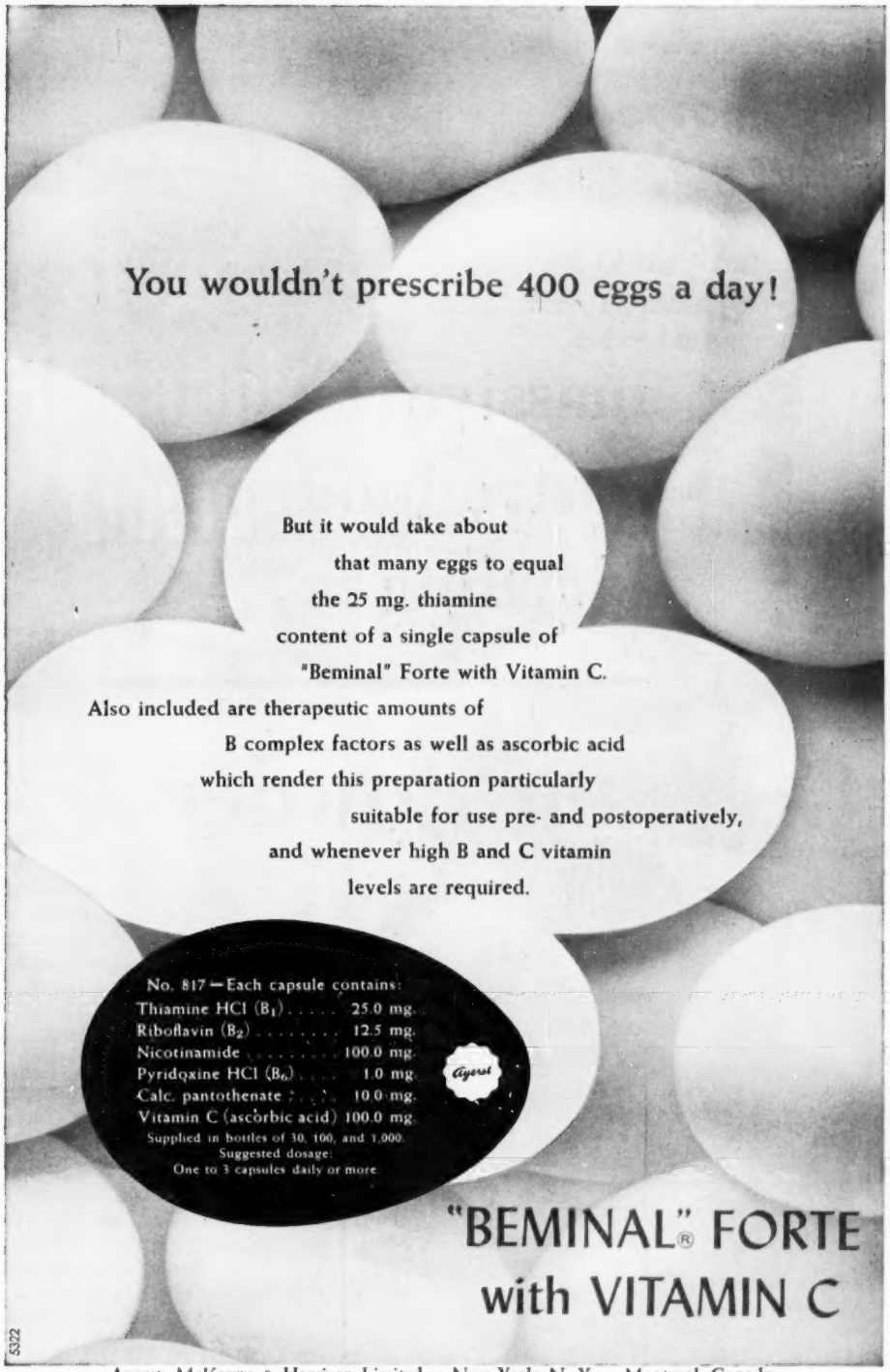

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THE CONSTANCY OF ACID VALUES IN A SERIES OF 227 PEPTIC ULCER CASES STUDIED BY REPEATED GASTRIC ANALYSES

SAMUEL MORRISON, M. D. AND MAURICE FELDMAN, M. D., Baltimore, Maryland

OUR INTEREST in this problem was stimulated by the fact that acid values in an individual may not fluctuate to any marked degree over a period of years. The fluctuations we have found are variable but tend to remain within the limits of the graded original acid values. The impression is gained from a review of the literature that acid values vary from time to time and that these fluctuations are marked and do not tend to return to their original level after adequate treatment. Contrary to this prevailing opinion, we have found that the acid values, in spite of the variable fluctuations noted from time to time, tend to return to fairly constant values as judged by numerous gastric analysis tests performed in the same individual over many years. In our study, it appears that the acid values for a large number of individuals tend to return to a previously determined level with little fluctuation in repeated tests. For this reason, this study is designed to direct attention to the constancy of acid values; it further emphasizes the importance of repeated gastric analyses performed over many years for this type of study suggests a reconsideration of the mechanism by which any individual's acid level seems to be characteristic and in many instances, constant for that individual.

Much objective information needs to be collected on acid gradation so that an appraisal may be made of the partly erroneous conception that acid secretion is easily influenced in any individual patient. Furthermore, a single gastric analysis may not clearly portray the patient's acid status. Repeated tests over a period of time are essential for the proper evaluation of acid values.

In reviewing the literature, the importance of a gastric analysis is predicated on the ability of the stomach to secrete hydrochloric acid. Although this may be basic and is of first importance, consideration has not been given to the acid value curve on repeated tests over a period of time.

In the evaluation of gastric analyses, we must bear in mind many factors which influence gastric secretion. Some of these are environmental influences, neuropsychiatric factors, various drugs and of course, food. As one example, both in theory and also in practice, it is widely held that the gastric acidity is permanently influenced by antacids. There is reason to doubt that this belief is actually supportable in many patients. In many patients the degree of acidity cannot be correlated with the activity of the ulcer. Cases could be cited in which low acidities are associated with ulcer symptoms and high acidities with remission of symptoms indicating that other factors than acidity alone are responsible for the activity of the ulcer and the production of acidity.

Gradations of acid values are commonly observed in repeated gastric analyses. For the most part, these variable gradations should be considered as a normal phenomenon of the gastric secretory phase, and should be discounted in the consideration of the grading of acid values since they do not fall within the significant limits. It must be pointed out here, that the acid values obtained in gastric analysis are approximate ones and often vary widely within normal limits. The acid value curve of repeated tests as stressed in our study is of more value than the results obtained in a single test. Variations in acid values in gastric analysis tests are known to occur from hour to hour and from day to night, as a result of various stimuli. There are also variations in different people and in the same individual from time to time. For this reason one should not rely upon the single test nor on the different variables that may be found on repeated tests, as long as the acid values followed the graded norm according to the graded chart presented subsequently.

Most statistics on gastric acidities have been correlated with age but not in the same patient who had repeated titrations as he grew older. In a study based on 227 patients, we were impressed with the observation that a considerable number have the same degree of acid value on repeated tests over many years.

Symptoms are often not paralleled by the degree of acidity. Patients may have high acid values with symptoms; these symptoms may disappear with the use of antacids. Later the same patients may have the same high degree of acidity without symptoms. Some of the patients occasionally have no symptoms with high acid values and contrarily have symptoms with lower acidity indicating that other factors are operating. Patients with symptoms correlated with elevated acid values and an ulcer may have the same acid values but no symptoms when the ulcer heals. It appears from the tables that the greatest number of constant hyperacidities are in the 1st degree hyperacid categories.

Of our 227 cases, there were 183 males and 44 females. The ages ranged from 19 to 78, the majority being in the second and fourth decades. Table 1 presents the cases according to age.

TABLE I

10-20	5 cases
20-30	55
30-40	75
40-50	54
50-60	22
60-70	9
70-80	1
Not specified	6
Total	227 Cases

Submitted Feb. 6, 1953.

In order to make a comparative study over the years, it is necessary to utilize a standard test meal. In our cases the test meal consisted of one slice of white bread and one glass of water. The importance of using the same test meal throughout the study is essential in obtaining consistent data for comparison studies.

The number of tests in each of our 227 cases is shown in Table 2. Most cases have had two or more tests.

TABLE II

2 tests	143 cases
3 tests	53 cases
4 tests	24 cases
5 tests	6 cases
6 tests	1 case

For a long range study of data relating to the constancy of grading test meals following gastric analyses we have tabulated the time intervals of study in our 227 cases. Table 3 shows the length of time the cases were studied. From this study, the findings show the time interval ranged according to the years the patient had had gastric analyses. The interval of the tests varied from one day to over 16 years. During this time as many as 6 tests had been made in a single case.

TABLE III

INTERVAL OF TIMES OF GASTRIC ANALYSES

1 day to 1 month	13 cases
1 month to 3 months	10 cases
3 months to 6 months	21 cases
6 months to 1 year	33 cases
1 year to 2 years	46 cases
2 years to 3 years	17 cases
3 years to 4 years	15 cases
4 years to 5 years	19 cases
5 years to 6 years	9 cases
6 years to 7 years	12 cases
7 years to 8 years	14 cases
8 years to 9 years	3 cases
9 years to 10 years	1 case
10 years to 11 years	7 cases
11 years to 12 years	0 cases
12 years to 13 years	4 cases
13 years to 14 years	2 cases
14 years to 15 years	0 cases
15 years to 16 years	0 cases
16 years to 17 years	1 case
Total	227 cases

Further study of our 227 cases included a breakdown of each case for the purpose of grading the results obtained in the gastric analysis. These were divided into four grades as follows:

Grade 1, free acid values ranging from 30 to 50 degrees

Grade 2, free acid values ranging from 50 to 70 degrees

Grade 3, free acid values ranging from 70 to 85 degrees

Grade 4, free acid values ranging from 85 to 100 degrees

In each case the degree of acidity was placed in the respective grade in order to determine the constancy of the degree of acidity and the variables. The results of this study are shown in Tables 4 and 5. In the constant group there were 154 cases. In these the degree of acidity remained constant throughout the time interval in which the tests were carried out. All have had two or more tests.

TABLE IV

THE NUMBER OF CONSTANT ACIDITIES IN 164 CASES TABULATED ACCORDING TO GRADES OF ACIDITY

Grade 1, Acidities were constant	98 cases
Grade 2, Acidities were constant	51 cases
Grade 3, Acidities were constant	5 cases
Total	154 cases

TABLE V

VARIABLE DEGREES OF ACIDITY OBTAINED IN 73 CASES RANGING FROM GRADE 1 TO GRADE 4

Acidities ranged from grade 1 to grade 2,	28 cases
Acidities ranged from grade 1 to grade 3,	10 cases
Acidities ranged from grade 1 to grade 4,	4 cases
Acidities ranged from grade 2 to grade 1,	19 cases
Acidities ranged from grade 2 to grade 3,	4 cases
Acidities ranged from grade 2 to grade 4,	2 cases
Acidities ranged from grade 3 to grade 1,	3 cases
Acidities ranged from grade 3 to grade 2,	2 cases
Acidities ranged from grade 4 to grade 2,	1 case
Total	73 cases

It is notable that 48 acidities varied in an upward direction whereas only 25 acidities varied in a downward direction. These variations were not consistently correlated with exacerbations or remissions although the general rule that lower acidities were more likely to be present in asymptomatic individuals was borne out.

SUMMARY

A study was made of 227 cases in which two or more gastric analyses have been performed to determine the variation of acid values charted over a period of time. The time interval varied from one day to over 16 years. In one instance as many as six gastric analyses have been made. In over one-half of the cases two tests have been made, while in over one-third of the cases 3 or 4 tests have been made. The acid values were divided into four grades. Although there have been variables, the majority fell into the range

of 1st and 2nd degree acidities. It is of interest to point out that of the 227 cases, there were 154 or 67.8 per cent in whom the acid values were constant over the observation period. In the remaining 73 cases, there were variable gradations of acidity. The literature does not lead one to believe that acid values often tend to be constant. On the other hand, it is generally thought that acid values are responsive to various agents and this is true within limits. However, the present study would indicate that the acid values tend to return to their previous levels.

11 E. Chase St., Baltimore, Md.

GASTRIC ULCER: ITS DIAGNOSIS AND DIFFERENTIATION BY GASTROSCOPIC AND ROENTGENOLOGICAL EXAMINATION

L. L. HARDT, M. D., F. STEIGMANN, M. D. AND A. WEISS, M. D., Chicago, Ill.

DESPITE THE great advances in roentgenological technics and in gastroscopic procedures during the past two decades, the differentiation between malignant and benign ulceration of the stomach is not always possible. Moreover, a gastric lesion itself is occasionally missed during an x-ray examination but seen during gastroscopy or vice versa. At times, too, a lesion is suggested by one or the other procedure, or by both, but no definitive diagnosis can be made. Such occurrences have led to a pessimistic attitude in some circles as to the diagnostic value of some of these newer technics. It is, therefore, of practical value to periodically evaluate the help the clinician may get from x-ray and gastroscopy in the diagnosis and differential diagnosis of gastric lesions.

In this paper, we will discuss mainly the value of x-ray and gastroscopy in the diagnosis and in the differentiation of gastric ulcerations when either method is used alone or both methods are used together. Possible errors in each method and their causes will be presented and suggestions for avoiding them will be made.

MATERIAL AND METHOD

The material studied consisted of 203 cases of gastric ulceration culled from several thousand cases of gastro-intestinal disease seen in a large charity hospital and in private practice. All of them had both x-ray and gastroscopic studies and the diagnosis of gastric ulceration was made by either one of the two or by both methods. Only the initial examination was considered in the preparation of the tables and discussion of results. Findings on repeat examination (either on x-ray or gastroscopy) are discussed later. Seventy-two of the patients from this group underwent surgery so that, in these, the accuracy of diagnosis as to presence and type of lesion was determined. The remainder of the patients were observed clinically for a period of time (one to five years) which we believed to be long enough to indicate the accuracy of the initial diagnosis as to the benign or malignant character.

RESULTS

Finding of Lesion: In the 131 patients who were treated only medically, the diagnosis of a gastric ulcerative lesion was made in 69 (52.67%) by both x-ray and gastroscopy. In 42 of them the diagnosis of the ulcerative lesion was made only by gastroscopy but not by x-ray and in 20, by x-ray only (Table I).

TABLE I

COMPARISON OF X-RAY AND GASTROSCOPY AS TO RECOGNITION OF PRESENCE OF ULCER

	Diagnosed by x-ray only		Diagnosed by Gastroscopy only		Diagnosed by both		
	No.	Percent	No.	Percent	No.	Percent	Total
Medical	20	15.2	42	32.0	69	52.76	131
Surgical	11	15.5	19‡	26.8	41	57.7	71
							202*

*Not included is one case in which ulcer was not diagnosed either by x-ray or gastroscopy.

‡In three of these ulcer was not proved on surgery: Surgery was performed beyond six weeks after gastroscopic diagnosis in two cases. Gastroenterostomy was performed in one case and presence or absence of ulcer was not reported.

In 72 patients who were treated surgically, the diagnosis of a gastric ulceration was made in 41 of them by both x-ray and gastroscopy. In 19, the lesion was diagnosed only by gastroscopy but not by x-ray, and in 11, it was diagnosed only by x-ray. This would suggest that in 61 patients of this group of 202, the lesion would have been missed if gastroscopy weren't done, while in 31, the lesion would have been missed if no x-ray and only gastroscopy alone were done.

Differentiation of the Ulcerative Lesion: Considering the value of x-ray examination and of gastroscopy in diagnosing the nature of a gastric lesion, i.e., whether benign or malignant, the following results are obtained. Of 56 cases which were proven benign on histological examination, 20 were reported as benign on x-ray examination. Nineteen were reported as malignant and in 17, no commitment was made in 22 (Table 2). In only 26 was there an agreement of the char-

TABLE II

DESCRIPTION OF ULCER BY X-RAY AND GASTROSCOPY IN 56 CASES PROVED BENIGN ON SURGERY

	Benign		Malignant		Undetermined		
	No.	Percent	No.	Percent	No.	Percent	Total
X-ray	20	35.7	19	34.0	17	30.3	56
Gastroscopy	22	39.3	12	21.4	22	39.3	56

From the Gastroscopy Clinic and Department of Internal Medicine, Cook County Hospital, the Departments of Internal Medicine, Stritch School of Medicine, Loyola University and College of Medicine, University of Illinois, Chicago, Illinois.

Aided by a Grant from the Hardt Foundation.

Submitted Feb. 12, 1953.

TABLE III

COMPARISON OF X-RAY AND GASTROSCOPY IN DESCRIBING THE NATURE OF THE LESION IN 56 CASES PROVED BENIGN ON SURGERY

X-ray and Gastroscopy Agree			X-Ray Benign Gastroscopy Malignant	X-Ray Benign Gastroscopy Undetermined	X-Ray Malignant Gastroscopy Benign	X-Ray Malignant Gastroscopy Undetermined	X-Ray Undetermined Gastroscopy Malignant	X-Ray Undetermined Gastroscopy Benign
Benign	Malignant	Undetermined						
11	5	10	1	8	10	4	6	1

acter of the lesion by the two methods (Table 3). Of nine cases proven malignant on histological examination, three were diagnosed as benign by x-ray, two as malignant and in four, no definite x-ray diagnosis was had. On gastroscopy, three of the cases were diagnosed as benign, four as malignant and one as undetermined (Table 4).

TABLE IV

DESCRIPTION AS TO NATURE OF ULCER BY X-RAY AND GASTROSCOPY IN NINE CASES PROVED MALIGNANT

	Benign*		Malignant		Non-Committal		
	No.	Percent	No.	Percent	No.	Percent	Total
X-ray	3	33.3	2	22.2	4	44.5	9
Gastroscopy	3	33.3	4	44.5	2	22.2	9

*In one case (28D) the ulcer was considered benign by surgical pathology and proved malignant on post-mortem examination.

DISCUSSION

Considering the recognition of the presence of a lesion, it is rather startling to find that, in a group of 203 patients with gastric ulceration, there was disagreement in 92 instances or in almost half of the cases between the findings by the two methods. The fact that 61 of the lesions were diagnosed only by gastroscopy and 31 of them only by x-ray examination is of grave importance to the clinician and requires careful evaluation of the reasons for this discrepancy. It, moreover, also stresses the need for doing the second procedure in cases where one is negative.

What were the reasons for failure to find the ulcers on x-ray examination?

The reasons for failure to detect on x-ray examination, a gastric ulceration which was later seen on gastroscopy and proven on surgery, are presented in Table 5.

TABLE V

REASONS FOR FAILURE TO RECOGNIZE GASTRIC ULCER ON X-RAY EXAMINATION IN NINETEEN SURGICALLY PROVEN CASES

Ulceration very superficial	13 cases
Crater filled with blood clot	1 case
Ulcer in healing stage	1 case
Pyloric obstruction causing distension of stomach	1 case
Reason not apparent	3 cases

It is readily seen that an ulcer crater which is very superficial will not retain sufficient barium to show the niche or fleck on x-ray examination and hence, the results of this examination will be reported as negative. Similarly, a crater filled with blood, and an ulcer in the healing stage will not permit the deposition in the ulcer niche of sufficient barium to be demonstrable on x-ray examination. Distension of the stomach to a degree of obliterating a not too deep niche is a well known possibility. In the three cases in whom no definite reason was apparent, a number of possibilities might be considered which are particularly encountered in an institution like ours, e.g., the social and educational status of the patient, the degree of preparation, time available for examination of each patient and last, but not least, the experience of the examining roentgenologist.

The reasons for failure to detect on x-ray examination gastric ulcerations which were later seen on gastroscopy, but which were not proven surgically because the patients were not operated upon are presented in Table 6. Essentially, most of them are not unlike

TABLE VI

REASONS FOR FAILURE TO RECOGNIZE ON X-RAY EXAMINATION GASTRIC ULCERS WHICH WERE LATER SEEN GASTROSCOPICALLY

Superficial or healing ulceration	18 cases
Small ulcer	2 cases
Ulcer with bleeding	2 cases
Swollen edges somewhat obliterating ulcer	1 case
Antral location	2 cases
Pylorospasm during x-ray examination	1 case
Cardiac site	1 case
Antral deformity on x-ray	5 cases
No apparent reason	10 cases

those in the preceding paragraph. Among this group of cases, however, some additional possibilities are encountered like the unusual site of the lesion and spasm or deformity of the antrum with its resultant masking of the ulcer crater. The ten cases of this group in whom no apparent reason has been found for missing the ulcer crater roentgenologically must be considered under the same possibilities as the similar above three cases.

While it is possible that some of the factors given as possible reasons for missing a gastric ulcer on x-ray examination might not be of sufficient importance under other circumstances, they are occa-

sionally met in our work and are, therefore, presented here.

In evaluating the results of the x-ray examination, one must consider the procedures in the particular x-ray laboratory. Too many gastrointestinal studies in one morning may result in a "let down" feeling by the roentgenologist during the latter part of the morning and may result in somewhat poorer diagnostic acumen. In some hospitals, particularly charity hospitals, there is, at times, poor rapport between the roentgenologist and the patient due to language difficulty or due to the fact that the patient is too ill to cooperate in the different maneuvers necessary for a complete and exhaustive fluoroscopy of the gastrointestinal tract. This may partially explain the 6.4 percent of cases in whom the reason for failure to detect the gastric ulceration on x-ray examination was not apparent. It might be worthwhile, however, to remember that Renshaw (1) reported that of a group of 150 patients showing a gastric ulcer on gastroscopy, ten had negative findings on x-ray examination. The other reasons, as superficial ulceration, blood clot filling the crater, or site of ulcerations, are all valid for missing the lesion on x-ray. Thus, Ivy (2) et al, too, state that the x-ray may overlook 5-10 percent of ulcerated gastric lesions provided small, non-penetrating and healing lesions are included.

What were the reasons for missing gastric ulcerations on gastroscopy?

Our reasons for missing the ulcerative lesion on gastroscopy when it was seen on x-ray and proven surgically, are presented in Table 7. They seem to be

TABLE VII

REASONS FOR FAILURE TO RECOGNIZE GASTRIC ULCER ON GASTROSCOPY IN ELEVEN SURGICALLY PROVEN CASES

Prepyloric site of ulcer	4 cases
Large edematous folds	2 cases
Hemorrhage	1 case
Hour-glass deformity	1 case
Pylorie site of ulcer	1 case
Ulcer situated on the posterior wall	1 case
Hypertrophic nodules	1 case

quite acceptable for failing to see gastroscopically a lesion which was seen on x-ray. Some of them are based on mechanical optical factors, e.g., blind spot areas, while others are due to changes of inflammatory nature which may mask and obscure a gastric ulceration.

The reasons for missing gastric ulcers on gastroscopy, which were seen on x-ray examination but not proven surgically, are presented in Table 8. These reasons are, in most instances, similar to those given above—e.e. on mechanical and inflammatory basis—the two cases which were thought to be diverticula presented deep craters without any inflammatory reaction around them and with comparatively clean bases and walls, so that ulcer was not considered. It is also possible that the craters had healed within two weeks

TABLE VIII

REASONS FOR FAILURE TO RECOGNIZE GASTROSCOPICALLY GASTRIC ULCERS WHICH WERE DETECTED ON X-RAY EXAMINATION

Ulcers situated on lesser curvature of antrum	6 cases
Atrophic gastritis "obscuring" picture	3 cases
Hypertrophic gastritis "obscuring" picture	3 cases
Ulcer designated as diverticulum	2 cases
Polypoid changes	1 case
Small niche on x-ray (10 days prior)	2 cases
No apparent reason	3 cases

so that they were not seen gastroscopically two weeks after having been demonstrated radiologically. Finally, in the three cases in whom no apparent reasons were given, similar possibilities to those given above for the unexplained radiological failures must be considered. However, here, again, one might refer to Renshaw's report (1) that of 170 patients in whom the true diagnosis was later established, there was disagreement as to correct diagnosis in 38 cases and that, in this group, nine benign ulcers were not seen gastroscopically, but only on x-ray. Shallenberger, et al (3), similarly reported that in one series of 16 gastric ulcers seen on x-ray, only eleven were seen gastroscopically.

It is generally acknowledged that gastroscopy has definite limitations which are both of technical and optical nature. The shape and size of the stomach, the activity of the stomach at the time of examination (peristalsis, spasms, external pressure and pulsations), the air distension and the blind spots all combine to make gastroscopy, at times, a difficult diagnostic procedure. Although the roentgenologist has technical difficulties, too, because of the patient's body build and other anomalies, his problem is, nevertheless, less difficult because he sees the entire stomach wall and not only the changing mucosa and he can prolong or repeat the examination at will. Considering these factors, it is understandable how some of the above enumerated reasons prevented gastroscopic visualization of a lesion found on x-ray.

The site of the lesion in the prepyloric area, high up on the lesser curvature or on the posterior wall, is an obvious reason for missing it, inasmuch as this region belongs to the gastroscopically inconstant or constant blind areas of the stomach. An abnormality of the stomach such as an hourglass deformity, also will prevent complete visualization of the interior of the stomach by the gastroscope. The presence of active bleeding during the gastroscopic procedure will certainly limit the time and value of this examination. The presence of polypoid changes or hypertrophic gastritis may, during marked contractions of the stomach, obscure a small gastric ulcer at the time of examination. On the other hand, it is possible to diagnose, occasionally, a large and deep crater as a diverticulum although the latter are much less common than ulcers. We are not able to explain the reason for missing the ulcer in the three cases with atrophic gastritis. In the two cases which had small niches on x-ray examination, gastroscopy was done ten days later during which time complete healing may have taken place (4).

DIFFERENTIATION BETWEEN BENIGN AND MALIGNANT ULCERATIONS

Considering the differentiation between benign and malignant gastric ulcers, we find the situation even more involved. Thus, in 65 surgical cases in whom a histological report of the lesion was obtained, a wide discrepancy existed between the clinical, roentgenologic, gastroscopic and pathologic diagnosis. It is significant that, despite many so-called criteria for differentiation between a benign and malignant ulceration, 5 of 56 benign cases were called malignant by gastroscopy and x-ray and only two of nine proven malignant lesions were thus considered by both methods. Individually, x-ray gave a correct diagnosis in only 22.2 percent of the malignant and 35.7 percent of the benign cases and gastroscopy in 44.5 percent and 39.3 percent respectively.

What were the reasons for the above mistakes on x-ray examination?

In 19 patients the reasons for a benign gastric lesion being considered malignant on x-ray examination were as follows:

Seven were described pathologically as large penetrating ulcers, adherent to surrounding tissue. Eight were characterized by marked induration around the ulcer and perigastric adhesions so that there was a mass-like appearance on x-ray. Two cases showed much scar tissue that was described as a filling defect on x-ray. In two cases, there was no apparent reason for the error.

In three patients the reasons for a malignant ulceration being considered benign were as follows:

In one case, the ulcer was small. Two cases had no apparent reason for the error.

In twelve cases the reasons for gastroscopy calling a benign lesion malignant were as follows:

In six of these patients, there was a polypoid or mass-like appearance due to edema or cicatrix formation. In three cases, the ulcer was large and penetrating. In two cases much bloody and degenerative material was present and in one, the pylorus was deformed due to adhesions.

In three patients the reasons for gastroscopy considering a malignant ulcer as benign were as follows: In one case the ulcer area had a nodular appearance and was diagnosed as hypertrophic gastritis. In one case, distortion of the angulus prevented adequate examination and in one case, there was no obvious cause for the error.

The various reasons presented above for failure to recognize and to differentiate gastric lesion by either x-ray and gastroscopy, point to the fact that there is still room for improvement in the technical procedure of both methods. Moreover, they stress the fact that the two methods are not competitive but are rather supplemental and complemental and that greater accuracy in diagnosis is achieved whenever both methods are used. Nevertheless, there are often cases in whom one or the other method is superior.

Thus, Schindler (5) considers that gastroscopy can best differentiate benign from malignant ulcers. Shallenberger et al (6) feel that gastric ulcers can be accurately described and classified by x-ray and that if the gastroscopist can see the ulcer, his information should bring the accuracy of differential diagnosis to about 95 percent. Others (7, 8), however, feel that, in many instances, gastroscopy fails to do this and that errors are committed both directions—benign ulcerations being called malignant and vice versa. Schindler (9) has discussed in detail, the value of gastroscopy in the differential diagnosis between benign and malignant ulcers and has equaled it to the microscopic examination—stating that it is even superior to the inspection of the gross specimen because in the gastroscopic appearance, the blood circulating through living tissue makes the gastroscopic picture plastic. He (9) and others (10) have attempted to describe gastroscopic signs which speak for or against a benign or for or against a malignant lesion. Nevertheless, the observations on the patients from our series support the findings in other series that in a moderate percentage of cases, all signs may be misleading and should, only with great caution, be considered as absolute and that, if any doubt exists, microscopic examination is still the better proof of the character of the lesion.

In the patients with proven benign ulcers a search for signs usually considered favoring a benign character showed these signs to be absent in a definite percentage. Six cases (10.7%) had no sharp edge without a surrounding wall; only two cases (3.6%) showed localized hemorrhages or pigment spots; only three cases (5.4%) had an arch shaped distortion of the angulus; only one case (1.8%) showed converging folds and in none did we see an hour-glass fold. On the other hand, the following benign cases showed signs suggestive of malignancy; six cases (10.7%) had nodular masses surrounding the ulcer; four cases (7.1%) showed a suggestive infiltration of the mucosa; three cases (5.4%) were located in the antrum close to the greater curvature; one case (1.8%) appeared in the prepyloric region; and four (7.1%) bled from the edge of the ulcer.

While 26.8 percent of the benign cases showed one or more of the last mentioned characteristics, three of the nine proven malignant ulcers failed to show those criteria in gastroscopy and thus, the diagnosis of benignancy was arrived at.

In this series of cases, our data confirm previous observations that the size of the ulcer, the presence of atrophic gastritis, infiltration of the mucosa about the ulcer, a callous or edematous wall, ragged edges, necrotic material on the floor of the ulcer, among others, neither confirm nor disprove the possibility of a malignant character of the lesion (8).

Since as stated above, microscopic examination of the lesion gives the only definite proof of the type of the lesion, it is fortunate that the recent introduction of the operating gastroscope (11) has given the clinician an additional method to differentiate benign from malignant ulcer short of exploratory laparotomy. To-date, the results of diagnosis from biopsies obtained through the gastroscope are still not commensurate with the results of other diagnostic procedures (6). This method, however, may, in the near future help

much in this differentiation when some mechanical difficulties in obtaining the biopsy and some technical ones in describing and interpreting the tissues are ironed out.

In the meantime, however, it might be worthwhile to remember that if one examination, x-ray, or gastroscopy is indefinite, questionable, unsatisfactory or differing from the results of the other method, a re-examination after intensive medical therapy for two to four weeks may frequently give the required results. Re-examination may cut down the percentage of error of the first examination and also the percentage of disagreement between the two methods. Renshaw (1) states, "when the x-ray and gastroscopic findings are not in agreement, further study and observation of the case is necessary, utilizing both "progress, roentgenologic and gastroscopic examination." With this, all clinicians must be in agreement as we heartily are. It must be mentioned, however, that, occasionally, "progress examination" may be misleading and results should, therefore, be carefully evaluated. Thus, of 25 patients who were regastroscoped by us, the original diagnosis—benign ulcer in 13 and malignant in four—was ultimately maintained. In four cases, the original diagnosis of malignancy was changed to that of a benign lesion. In one case an ulcer originally called benign was finally diagnosed as malignant.

In the remaining three patients, however, repeated gastroscopy was misleading. In one instance of a poorly healing large gastric ulcer, the original diagnosis of benignancy was correct but follow-up observation led to an incorrect diagnosis of malignancy. On microscopic examination after resection of this lesion, the benign character diagnosed initially was confirmed. In one instance, four follow-up gastroscopic examinations revealed a progressively healing gastric ulcer, yet on surgery an infiltrating mucous adenocarcinoma was found. In another instance, the initial impression of malignancy was affirmed by two repeat examinations, but the histologic examination proved the lesion to be benign.

SUMMARY

On the basis of our review of 203 cases of gastric ulcerative lesions we believe that no patient with gastric symptoms should be considered as having an adequate check-up unless gastroscopy has been performed. This holds particularly true if the x-ray examination has resulted in a negative or indefinite finding. Among the latter must be included the failure of differentiating between a gastric ulcer or carcinoma on x-ray. The use of both methods—x-ray and gastroscopy—is advantageous in that the two methods supplement each other and a higher index of accurate diagnosis is obtained. In some instances, the x-ray and in others, the gastroscope gives a higher degree of accuracy, but neither method alone is superior to the two methods used jointly. The clinician should keep in mind that the patient will profit most by the use of both methods. Re-examination by both methods after intensive medical therapy is indicated in all questionable cases.

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THE CONCEPT OF PERIODICITY IN THE NATURAL HISTORY OF PEPTIC ULCER AND ITS CONSEQUENCES

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THE PERIODICITY in the evolution of Peptic ulcer seems to have already been observed by the ancient authors (Hippocrates, cited by Rosenak and Crohn) (1). In the late 19th century it was well described by Bucquoy (2) in his studies of duodenal ulcer. Thereafter, for a long time, periodicity was forgotten or considered as an accessory symptom. It is only in 1908 that Graham (3) reemphasized its importance. Moynihan (4), Crohn (5), Gutmann (6) described the periodicity in ulcer as an outstanding feature of the disease. Cole (7) was among those who

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demonstrated that the ulcer heals rapidly after the attacks. Jahiel (8) made a comparative study of the rhythm of epigastric pains in various diseases and analyzed the specific characteristics of each type of attacks. Moutier (9) in a series of 628 cases, and Emery and Monroe (10) in a study of 1465 cases, indicated statistically the overwhelming frequency of the phenomenon of periodicity in peptic ulcer. This fact has been stressed in the last few years by the majority of workers in the field; it has been repeatedly emphasized by Andresen (11), and is now universally admitted. However its importance in the study of the pathogenesis of the disease has been usually overlooked. In this article we shall analyze the modalities of evolution of peptic ulcer and then apply the concept of periodicity to a critical review of the pathogenic theories and management of the disease.

(A) Natural History

The description which follows has been based on the analysis of 50 cases of gastro duodenal ulcers (18 ulcers of the lesser curvature of the stomach; 5 pyloric ulcers; 25 duodenal ulcers; 1 post bulbar ulcer; one case of double ulcer—stomach and duodenum). The patients were observed during a period varying from 2 to 25 years. A diagram of the evolution was established for each case; the corresponding variations of the x-ray picture were noted. Surgery was performed in 32 of these cases for various reasons. In 45 of these cases it was possible to observe the typical periodicity and the various events of the natural history of peptic ulcer described below. In one case (the post bulbar ulcer), a perforation occurred at the end of the first active episode of the disease, and, after suture, was followed by a non-systematized dyspeptic syndrome which was explained by the partial duodenal stenosis and perivisceral reaction following operation. In 4 cases (4 duodenal ulcers), there was a superimposed disease (hepatobiliary disease or gastritis), which had an evolution concomitant to the ulcer, seemingly modifying its periodical picture; however, it was possible, in these cases, to differentiate the intermittent ulcer attacks from the superimposed dyspeptic syndrome.

1) Signs and Symptoms

Peptic ulcer progresses through a succession of attacks and recoveries.

Characteristics of the Attacks

The ulcer attack averages 15 days to 3 weeks, although some individuals have longer or shorter attacks. It has a sudden unpredictable onset and a sudden unpredictable end. During this active stage there are daily occurrences of pain.

Pain in various modalities (cramps, burning sensation, etc.) represents the unique symptom. Its intensity is variable. It may be transfixiant, radiating to the back. Nocturnal pains are observed frequently. Pain may start shortly after meals or may be more tardive. None of these last characteristics, however, the nocturnal occurrence of pain, its irradiation to the back, its post-prandial rhythms are typical of ulcers; they may be present in many other diseases, for instance in referred pain originating from an appendicitis.

Characteristics of the Interval—Free Periods

The duration of the free intervals is variable but is always longer than the attack. A given pattern of attacks and recoveries is rather characteristic of the disease for a given individual, although sometimes, wide variations can be observed. During the free interval, the patient well tolerates a normal diet.

Various reasons have been given for the return of the attack. None of them have been satisfactorily substantiated by facts. One can say that in peptic ulcer disease recurrences do not seem to depend on any patent change in the external environment, and particularly, do not depend on the nature of the diet.

In diseases other than peptic ulcer, involving the upper abdomen, the progression of symptoms is quite different. *Paroxysmal hepato-biliary attacks* may occur periodically with free intervals of variable length in between. These attacks are of *short* duration: several hours to one to three days. The brevity of the episode contrasts with the long attacks ordinarily lasting several weeks in peptic ulcer. *Dyspepsias, or epigastralgias of nervous origin, or due to indigestion, or due to gastritis* offer no systematized picture. The patient may suffer 2 or 3 days, then feel better, then suffer again. The pain recurs after some changes in the diet or after nervous strain. This dependency of pain contrasts with the indifference of peptic ulcer to changes in the external environment. It explains the impossibility of assigning a pattern of evolution to this group of diseases. *Ulcerations* accompanying a gastritis or following a stress, or due to injuries to the nervous system etc., do not show any tendency to periodical recurrence. The disease is usually rapidly self limited. Pains or discomfort in *cancer of the stomach* have no periodical evolution. They may be more accentuated at certain periods of the evolution of the disease, but they seldom disappear completely. They are characterized by their insidious onset and evolution. *Referred epigastric pains* have an irregular pattern which follows the fluctuations of the causative disease (cholecystitis, appendicitis, ovarian disease, etc.).

X-ray Studies

The radiological signs are very apparent during the ulcer attack. They translate the presence of the ulceration (niche), the spasm which participates locally to the constitution of the niche, the edema of the mucosa with its characteristic deformities, the hyperactivity of the peristalsis, or, sometimes, the atonic state of the stomach or duodenal walls. *These x-ray signs have a tendency to disappear during the free intervals*, due to the recession of edema and the healing tendency of the ulcer. They reappear when the attack recurs. This contingency of radiological signs in a benign ulcer represents the best element of differentiation with a malignant lesion. However, as we shall see later, an old ulcer, although benign, may be translated by fixed non-reversible x-ray deformities. In other cases it has been observed that a benign ulcer occurs on a cancerous floor, thus having its characteristic periodical evolution independent from the concomitant progressive evolution of the cancer at the same place (11a). This emphasizes the importance of the study of other

characteristic deformities, irregularities of contour, segmental rigidity, incarcerated niche, plateau niche, meniscus sign which not only translate the infiltration of the gastric wall by cancer and are permanent, but have a tendency to increase in size if cancer is present. These studies are facilitated by the use of special technics, such as mucosal fold studies, stereoradiography, pharmacoradiography, gastric insufflations.

LABORATORY STUDIES

The laboratory is not particularly helpful in the diagnosis of the disease. High gastric acidity is far from being always encountered in peptic ulcer. Cases with low acidity have been reported, especially in gastric ulcers. This question will be discussed later under pathogenesis. Blood may be present in the stomach or duodenum of ulcer patients during the active stage of the disease and is usually absent during free intervals. The cytological diagnosis of smears of gastric contents is not considered yet as a routine examination, although recent technical improvements seem to have rendered the method more accurate (11b).

GASTROSCOPY

This exploration is a good adjuvant to the diagnosis. After identification of an ulcer through the gastroscope during the active stage of the disease, the same exploration made during the free interval may show the complete transitory healing of the lesion (11c).

2) EVOLUTION

The picture of the disease may remain unchanged and may persist for years with the same unmodified pattern of attacks and recoveries. (Fig. 1.)

In rare cases the attacks may become less frequent, less severe and, eventually, the disease may disappear spontaneously. Usually, as the ulcer is becoming older, the frequency of the attacks increases with shortening of the free intervals. When at the same time the symptoms are more accentuated and the duration of the attacks is prolonged the ulcer may be called virulent, (Moore). At a later stage the periodicity may fade more. An old virulent, progressive ulcer exteriorizes, adheres to the adjacent organs. A localized plastic peritonitis is organized. Pain becomes constant and the radiological signs have a tendency to become permanent. (Fig. 2) (Cases No. 1 and 2).

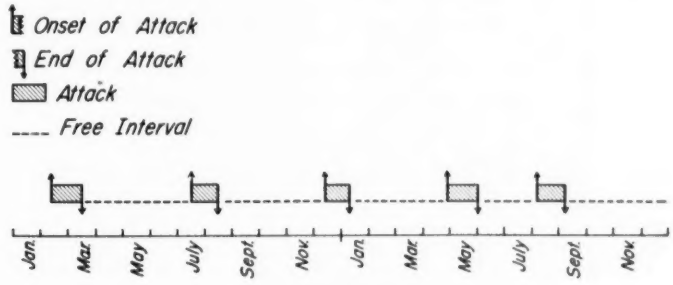

Figure One

Uncomplicated Ulcer

3) COMPLICATIONS

Complications may occur at any time during the evolution of a peptic ulcer. Certain of these complicating events do not alter the periodicity of the disease. They begin and terminate with the ulcer attack. We should consider such so-called complications as being closely linked with the pathogenic mechanism involved in ulcers. The others are true complications and they markedly change the pattern of periodicity of the disease.

We have already said that *exteriorization* of the

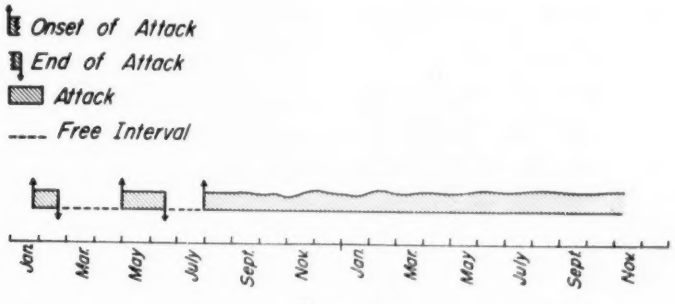

Figure Two

Virulent Ulcer

ulcer changes the periodical rhythm of the disease as it alters its anatomical and radiological characteristics.

Hemorrhages may occur in the middle of an active episode. They suppress further clinical manifestations of the attack, namely the pain, thus seemingly shortening the duration of this active episode; the lesion, however, continues its inapparent cycle. Hemorrhages occurring at the onset of an attack suppress all other clinical manifestations, hence represent "equivalents" of the attack. Such hemorrhagic equivalents may occur from time to time or replace all other signs and symptoms at each attack. This last form of periodical digestive bleeding, translating the evolution of a peptic ulcer, is not uncommon; its diagnosis may be difficult to establish, inasmuch as the radiological signs of a bleeding ulcer are most of the time extremely discrete.

Perforations may occur in the course of the disease or as a first manifestation. When a perforation has been treated surgically by simple suture it is usual to observe a change in the pattern of the disease, and even, in a few favorable cases, an absence of recurrences indicating that the disease possibly has been brought to an end.

Stenosis, particularly at the pylorus, is of two kinds. The most common one is represented by an organic narrowing of the canal due to sclerotic reaction of the ulcer and is an irreversible phenomenon; the stenosis adds its proper signs and symptoms to the disease and alters its periodical picture. In other instances the stenosis is due to the edematous reaction of an ulcer during its active stage; the phenomenon is reversible thus disappearing with the end of this active episode and leaving unchanged the diagram of periodicity. Spasm plays a minor role in the mechanism of such remittent stenoses.

There are other forms of *gastric retention* (12) which can occur in the presence of a *widely patent pylorus*, with no stenosis whatsoever along the gastroduodenal tract, the ulcer being located anywhere in the stomach or duodenum. Their mechanism involves a sudden and complete loss of tonicity of the gastric or duodenal walls. When they occur they accompany the ulcer attack, disappearing with the end of the active episode, thus not altering the periodicity.

Gastritis may coexist with ulcers. Its origin is not uniform. In some cases it represents a superimposed disease due, for instance, to alcoholism, or abuse of drugs. When such a gastritis occurs it tends to render less precise the periodical evolution. In other cases, a diffuse or localized gastritis, frequently hemorrhagic, appears during the active stage and disappears with it; hence it does not alter the periodical evolution of the disease. This last form of gastritis, linked to the ulcer process, is still unknown in its pathogenesis.

The possibility of *malignant transformation* is a subject of controversy. In the opinion of the writer, malignant degeneration of an ulcer is not likely to occur. A cancer may start its growth on the edges of an ulcer crater or elsewhere on the surface of the gastric mucosa. This growing cancer, however, causes changes in the pattern of evolution of the ulcer which must be detected as soon as they become apparent.

In summary, the natural history of peptic ulcer is dominated by the concept of periodicity with the specific clinical and radiological characteristics attached to it. The pattern of this periodicity may change due to the occurrence of various complications. Still this pattern is the best element on which a positive diagnosis of the disease can be established. It represents an excellent asset in the differential diagnosis of peptic ulcer and in the detection of complications. It has also to be considered for the timing of diagnostic procedures.

B) THE CONCEPT OF PERIODICITY IN RELATION TO THE PATHOGENIC THEORIES OF PEPTIC ULCER

The periodical evolution is such a striking and constant finding in the natural history of peptic ulcer that it must be linked to an important factor in the mechanism of the disease. Yet this concept has frequently been overlooked or misinterpreted in the pathogenic theories of ulcer by the various workers in the field who have considered the persistence and chronicity of experimental ulcers in animals as the criteria for true peptic ulcers. It is our belief that such experimental work should closely follow the natural history of the disease in man. Criteria should include not only the formation of an ulcer with its anatomical characteristics, but also the production of a remittent and recurrent disease.

We shall critically review the various theories of peptic ulcer from the standpoint of their ability to explain the periodical features of this disease.

One of the most widely adopted theories is that peptic ulcer is a disease of *gastric hyperacidity*. The acid regurgitation and the burning sensation in the epigastrium have been linked to this high acidity. The symptoms and discomfort are rapidly relieved by alkalies. The gastric juice has frequently been found hyperacid after intubation. In the experimental field it was possible to produce, in animals, ulcerations of the digestive tract through various technics deviating the course of digestive secretions; or by suppression of certain secretory zones thereby modifying the normal physiological neutralization of gastric juices. The neutralizing action of mucin was also investigated both clinically and experimentally: the alkaline, buffering action of gastric mucus was found to be, possibly, modified or suppressed by the hyperactivity of lysozyme in ulcer patients. Several criticisms can be made, however, of this theory of hyperacidity. Besides the fact that hyperacidity is found, as well, in other diseases of the digestive tract which bear no relationship whatsoever with peptic ulcer, and is also found in normal persons (13), we know that acidity curves in a given ulcer patient do not follow the fluctuations of the signs and symptoms of the disease (14). Furthermore, all the derivation technics used experimentally, from the classical experiments of Mann and Williamson (15) to the very recent procedures by Dragstedt (16), which all aim to the change of gastric acidity, produce progressive ulcers at the first stroke, with all the characteristics of an inflammatory lesion, but with no spontaneous healing tendency and periodical evolution: hence they reproduce a lesion similar to certain aspects of the post operative marginal ulcer but not comparable to the periodical ulcer as it occurs in man.

Another theory is based on *psychogenic factors*. In its most widely accepted form, this theory implies that

an ulcer attack follows certain types of psychological situations occurring in patients with a certain personality pattern (ulcer personality). This theory would allow several interpretations of the periodical recurrences: 1) Cyclic changes in the patient's psychological status: such changes have not been reported in ulcer patients (17, 18). 2) Periodically recurrent psychological traumas: although several cases in which ulcer followed a psychological trauma have been reported, in other cases, similar studies were negative, and careful search revealed that the same kind of psychological trauma was present during free intervals. To be valid such studies should demonstrate that a given type of psychological trauma precedes all recurrences and is absent throughout the free intervals. 3) Cyclic changes in the resistance of the gastric mucosa to nervous impulses: there is very little data concerning this point; the difficulty in interpreting the effect of emotional stresses on gastric mucosa has been borne out by recent studies. Although it has been demonstrated that emotional stresses act on the vascularization of the gastric mucosa, no relation, whatsoever, could be established between the vascular manifestations and specific gastric symptoms or disorders (19). In summary, no factor linked with the psychogenic theory has been demonstrated which would be absent during the long free intervals and be present only just before the onset of the attack.

The hormonal theory of peptic ulcer, linked, in part, with the psychogenic one, has recently been revived as a result of observations on certain effects of drugs like ACTH or cortisone. The facts can be summarized as follows: Selye (20) demonstrated experimentally that acute gastric ulcers can be produced by repeated stresses. This author linked the gastric manifestations to the over function of the adrenals. Gray and his co-workers (21) recently observed that repeated administration of ACTH or cortisone considerably increases the secretion of pepsin and hydrochloric acid, thus establishing a relationship between the pituitary-adrenal function and the stomach secretion. As a result of such increase in pepsin and acid, aggravation of peptic ulcers occurred and acute ulcers in normal persons or exteriorization of clinically inapparent ulcers were produced. One is entitled to conclude from these observations that acute ulcerations can be produced, or peptic ulcers can be aggravated by the hypersecretion of certain cortical hormones. But "the exact relationship, however, between the acute gastro duodenal erosions and chronic peptic ulcer in man has not yet been clarified" (Gray). Another possible effect of components of the adrenal cortex secretions can be considered: Dougherty and Schneebelli (22), Ragan (23), and others reported that besides its antiphlogistic action, cortisone has also an inhibitory effect on healing activity. Hyperactivity of the adrenals could therefore favor the chronicity of the ulcer by interfering temporarily with the healing tendency of the gastric and duodenal mucosa. When this hyperactivity would cease, the equilibrium of forces involved would be re-established and healing occur. Still one would have to find the reasons for such periodical fluctuations of adrenal function in ulcer patients.

A vascular disturbance somewhere in the gastroduodenal wall could explain the localized ulcerative lesion. Arteriosclerosis involving one or a group of small arterioles could provoke a localized ischemia and a crater would be rapidly formed. The gastric juice would act on this ulceration interfering with the healing and creating a chronic lesion. Arteriosclerosis, however, seldom occurs in the gastric arteries and is not encountered in young individuals whereas peptic ulcer usually is. Syphilis or diabetes could, in young people, play a role in the production of arteritis but this etiology could only explain the occurrence of a minority of ulcers limited to diabetic or syphilitic patients. It is still possible that an arteritis is at the basis of the phenomenon but its etiology remains to be found. The disease, peptic ulcer, having a periodical evolution with healing tendencies between attacks, would require a reversible and recurrent vascularitis to explain this process.

Anaphylaxis and allergy have been considered as possible pathogenic mechanisms. Various external allergies and food hypersensitivities have been incriminated. No satisfactory evidence of the role played by such exogenous allergens has, however, been given, although various successful attempts have been made to produce ulcers experimentally through such mechanisms. Anaphylactic reactions in the passively sensitized stomach of dogs and monkeys were produced following intravenous injection of the antigen (24, 25); cytotoxins were used to produce gastric lesions (26, 27); anaphylactic reactions of the Arthus type were described in the stomach of generally sensitized animals by various observers (28, 29, 30). None of these experimental techniques have been able to reproduce the periodical evolution.

Many years ago *focal infection* was taken as a cause of peptic ulcer (31). A chronic streptococcal infection of the mouth was considered as a responsible agent. Treatment of these focal infections was not capable, however, to eradicate the lesion. The theory was, again, unable to explain the natural course of the disease.

Various other pathogenic theories have been proposed. A number of experimental techniques, in addition to the ones already described, were tried and it can be said that most of them were successful so far as the production of a gastric lesion (erosion or ulceration) was concerned. One comes to the conclusion that it is apparently not difficult to produce an ulceration in the experimental animal. The problem which requires an answer, however, is quite different. As peptic ulcer is a lesion which heals spontaneously after completing a given cycle and *recurs again periodically*, a mechanism should, therefore, be found which would not only produce the anatomical lesion, but also explain its healing tendencies and periodical recurrences and, eventually, certain of its complicating events. A theory was presented in 1938 (32) in connection with this problem. An experimental work, started before the war, was resumed, by the author of this article, in 1949. The theory is based on the role played by a *local autoantigen* (modified gastric mucosa), which would be reformed in situ periodically and cause alternative phases of sensitization and desensitization. Such an intermittent immunological phenomenon could explain the periodicity of the disease and could account for its indifference to external factors. These studies are still in progress (33).

Peptic ulcer can be included in a group of diseases

which either are characterized by periodical recurrences, as in certain forms of conjunctivitis, iritis, glaucoma, gout, certain forms of periodical cerebral edema, menstrual allergies (paroxysmal menstrual migraines or liver attacks), ulcerative colitis, and perhaps, malaria in its chronic paroxysmal manifestations; or show unexpected relapses which cannot be satisfactorily explained by a reactivation of the primary causative agent, as can be observed in glomerulonephritis, rheumatic heart disease and hepatitis. Several years ago it was thought (34) that these very disparate diseases could be interrelated by a common pathogenic mechanism in which an autoantigen would play an essential role. An extensive clinical and experimental research based on this hypothesis, has been performed by a large number of investigators, in this country and abroad, especially during the last ten years. It has brought a considerable amount of documentation (35, 36, 37, 38, 39, 40, 41). Good evidence of a possible pathogenic role played by an autoantigen has been supplied in a few diseases (phacoanaphylaxis, menstrual allergies, certain forms of hemolytic anemia). In many other entities, however, like glomerulo-nephritis, recurrent hepatitis, rheumatic heart disease as well as peptic ulcer, the problem is still under investigation and no definite proof of the role of an autoantigen has yet been advanced. Recently, Reimann (42) described, under the name of periodic disease, a group of symptom-disease complexes including cyclic fevers, periodic edemas, intermittent neutropenia, certain types of arthralgias, etc. in which the periodicity of evolution is more regular, the recurrences more frequent and more accurately predictable than in the group of diseases above mentioned. Both groups have in common: 1) the absence of well established reason capable of explaining the recurrences, 2) the lack of progressiveness of the lesion, at least for a given period of time.

C) The Concept of Periodicity and the Management of Peptic Ulcer

There are several approaches to the therapy of peptic ulcer. The aim of these approaches may be: (1) a curative treatment on an etiological basis, which will prevent the recurrences of the disease; (2) a treatment which will shorten the attacks and/or alter the periodical evolution; and (3) a treatment toward alleviating the symptoms. Unfortunately there is no etiological treatment of peptic ulcer as its cause is still unknown. The evaluation of the treatment directed toward shortening the attacks and/or altering the periodicity is made difficult by the self-limited tendency of the attacks and the presence of long free intervals. Statistical studies with long term follow-ups (several years) of the symptoms can give a trend of opinion but no complete demonstration; the differences in the pattern of periodicity between different individuals, as well as the less marked differences in the same individual over a period of years, and the possibility of lack of correspondence between the evolution of the lesion and that of the symptoms have to be taken into account in such studies. Personal experience and review of the literature of these last 30 years give no indication that the first two approaches above mentioned have been met successfully by medical treatments. Therefore this chapter will deal with a variety of therapeutic concepts which are not specific and act primarily by alleviating the symptoms.

The treatment of peptic ulcer has to be considered differently during the active episodes and the free intervals of the disease.

During the active phases: Bed rest and a modified Sippy diet, together with antispasmodics are indicated, for the first days or the total duration of the attack. Several years ago Winkelstein recommended the use of a continuous alkalinized milk drip into the stomach in severe cases.

In between the attacks: A special diet is usually prescribed. It seems that in uncomplicated ulcers with spontaneous tendency to heal, with no superimposed gastritis or any other disease of the digestive tract, a normal regimen could be acceptable as well as in between the attacks, and would not change appreciably the course of disease. The unnecessary prolongation of a milk diet together with absorbable alkalies has been responsible for accidents of hypercalcemia, calcinosis and aggravation of renal insufficiency (43), (Case No. 3).

Various drugs have been proposed for the medical treatment of peptic ulcer. Absorbable alkalies given moderately, aluminum gels; bismuth; resins; mucin; antispasmodics; antihistaminics, injectable histidine (given as anti-shock therapy); enterogastrone; "banthine," "prantal" and "antrenyl" (anticholinergic drugs); "kutrol" (extracted from the urine of pregnant mare) represent a variety of treatment based on very disparate concepts. They improve the symptoms sometimes very appreciably. In the present status of unknown etiology of the lesion they cannot be expected to have curative properties. Therefore, the patient must remain under medical supervision even if he feels better, because of the possibility of recurrence or sudden complication.

Surgery is indicated only in complicated cases. Moore and his co-workers (44) have recently defined the primary and secondary criteria on which to base the indications for surgery in duodenal ulcers. The existence of a virulent, progressive, non-remittent ulcer is one of the most important of these criteria. They can also be applied to gastric ulcers. In gastric ulcer the possibility of a superimposed malignancy renders even more important the study of clinical and radiological changes in the semeiology of an ulcer. The quality of the surgical results largely depends on the correct and prompt evaluation of these changes.

Various types of subtotal gastrectomy have been proposed by Billroth, Polya, Finsterer, Hoffmeister, Madlener, Judd and others, including the recent suggestions of Dragstedt based on experimental research. Gastrectomy, when it removes all the ulcer zones, can be considered as a radical treatment. When, for various reasons, gastrectomy leaves the lesion in situ, it acts in a way which remains to be fully understood. The current opinion is that it acts by suppressing or considerably lowering the acidity, and by deviating and accelerating the emptying. This action would be comparable to the effects of a simple gastroenterostomy but it is more complete. It seems difficult to admit such a mechanism of action without discussion: Is the

change in the acidity such an efficient therapeutic factor? The answer would be "yes" so far as the complications of the ulcer are concerned (gastritis, periulcerative secondary lesions); it would be "no" if we consider the ulcer itself which, for a long time before operation, healed rapidly and repeatedly in the presence of acid chyme. On the other hand, the rate of emptying in many types of successful gastrectomies is not very different from the rate of emptying through the pylorus before operation. The diversion of food from the site of the lesion also cannot be considered as an indisputable factor as, in many cases, a reflux through the afferent loop of anastomosis is present which brings the food in contact with the lesion. Therefore, to explain the efficiency of subtotal gastrectomy one would have to think of other possible factors such as neurocirculatory or tissue changes occurring after the operation.

Vagotomy alone or associated with gastro enterostomy or antrectomy or gastrectomy has been proposed. Its therapeutic value is debated. Before discussing further this procedure we would like to stress that, at the present time, not enough experience has been accumulated on the possible tardive effects of vagotomy. "Since it took 10 years or more to uncover the ill effects of gastroenterostomies, obviously it is much too soon to appraise the eventual consequences of vagotomy. The direct effects, in the long run, on the stomach, liver, pancreas and small intestine, to say nothing of the indirect effects on the vascular system with the influence of the parasympathetic system obliterated, remain to be carefully evaluated." (Boles). In view of such possible implications, the indications for vagotomy should be always, and for each case, clearly justified (44a). Vagotomy depresses gastric acidity. Used alone, in a noncomplicated remittent ulcer, in which hyperacidity plays no role in the determination of periodical recurrences, vagotomy is unable to protect against further evolution of the disease (45). Used together with simple gastroenterostomy, for non-extirpable duodenal ulcers, it seems to have given satisfactory results (46). The evaluation of these results still needs further studies and longer term follow-ups. Used together with gastrectomy, vagotomy may prevent certain complications at the level of anastomosis. When the postoperative lesion is already produced, one must make a distinction between two types of diseases occurring in a loop of anastomosis. One type is characterized by a progressive jejunitis accompanied or not by ulceration; its etiology is linked to the irritative action of gastric juices; vagotomy would be indicated in this type of lesion (47). The other type of postoperative anastomotic lesion behaves like a true peptic ulcer (48), and is usually located in the efferent loop of anastomosis; primarily this ulcer may be caused by trauma and, probably, the action of gastric juices; rapidly, however, a periodical evolution is observed, with alternatives of healing and recurrence, which does not depend any more on the acidity (49); hence vagotomy alone does not find its justification in this second type of postoperative lesion which requires more definite surgery.

One point must be mentioned in connection with the problem of surgery in peptic ulcer. It concerns ulcers which are brought to surgery for various reasons (virulence, repeated hemorrhages, etc.), and are not found at the surgical exploration. This happens when the ulcer is hidden in the posterior wall or when it is operated during a free interval of the disease when it cannot be detected because of transitory healing. In such cases it is important to give their full value to the clinical data. If a definite periodical history of ulcer exists in the past history and signs of ulcer have been found on the x-ray plates, complementary maneuvers of exploration are indicated as, for instance, a gastrostomy or a duodenotomy or the mobilization of the duodenal angle to try to find a posterior duodenal ulcer. If no ulcer is found whatsoever, it would seem difficult to proceed further with the operation. The patient should, nevertheless, remain under observation and be explored at another time, nearer to an acute episode of the disease if the symptoms persist and the diagnosis is again clinically confirmed. (Case No. 4).

CONCLUSIONS

It is well established that a periodical pattern of attacks and recoveries characterizes the natural history of peptic ulcer. The attacks are of 2 to 6 weeks duration with daily symptoms, separated by long free intervals of months or, occasionally, years. Analysis of the periodical pattern together with the other characteristics of the attacks is a valuable adjuvant in the differential diagnosis of peptic ulcer from other relapsing upper abdominal syndromes. One must not be misled by apparent deviations from this periodical pattern. Factors like a superimposed disease or the occurrence of complications may alter the periodical evolution of the disease by changing the duration of the free intervals, the duration or the nature of the recurrent attacks or by adjunction of a new set of symptoms. The complications of peptic ulcer, in connection with their ability of modifying the periodical pattern of the disease, can be divided into two groups: In the first group (transitory edematous stenosis, transitory gastric atony, and certain forms of diffuse hemorrhagic gastritis), the periodical pattern remains unchanged. In the second group (secondary gastritis, perivisceritis, stenosis, hemorrhage, acute or chronic perforation, development of carcinoma), the periodicity is partly or completely changed.

The constant occurrence of a characteristic periodical pattern in peptic ulcer and its absence in other gastric or duodenal erosions or ulcerations indicates that a periodically recurrent factor must play a role in its pathogenic mechanism. Review of the available data shows that none of the suggested etiological factors has yet been shown to vary according to the changes in the activity of the disease. The absence of clinically demonstrable external causes of recurrences leads to a search for an internal factor, capable of periodical variations. The factor causing the recurrences may not be necessarily the same as the one initiating the disease.

The criteria for the experimental reproduction of peptic ulcer should include not only the obtaining of the anatomic lesion but also the reproduction of the intermittent evolution, with complete healing between periods of activity.

The treatment of this clinical entity is only symptomatic at the present time. Various surgical proce-

dures have been suggested, for the management of complicated cases. Their rationale is discussed.

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CASE REPORTS

The four cases reported below illustrate the importance of the periodical behavior of the ulcer disease for the timing or the justification of therapeutic measures.

Case No. 1—(No. 46581).

M. M. 56 year old male. Was first admitted to Montefiore Hospital in March 1949. This patient had a history of fibronodular lung tuberculosis of both apices which was diagnosed in 1949, following several years of chronic cough. Since 1948 there were repeated positive sputa. In 1950 he had an episode of pleural effusion and some progression of the parenchymal lesions.

His digestive symptoms started in 1932. Since then he has had, every year, 3 or 4 attacks lasting 3 to 5 weeks, consisting of epigastric pains 1 to 3 hours after meals with, from time to time, vomiting of food. X-ray findings at the beginning were not contributive, no diagnosis of peptic ulcer could be made although the history seems to have been quite typical. In 1945, for the first time, an episode of gastric bleeding occurred. The patient was followed in 1949, 1950 at Montefiore Hospital. A good record of his attacks could be obtained while in the hospital. In 1949, he had 3 attacks separated by long free intervals. In 1950, he had in April one attack. Then, starting in August 1950, he had repeated attacks, lasting several weeks, of epigastric pain which became more and more acute, with frequent vomiting of food and loss of weight. The free intervals were shortened and lasted 2 to 3 weeks at the maximum. In December 1950, the patient had a massive hematemesis which terminated an attack of excruciating pain which had lasted 3 weeks. X-rays taken in January 1951 showed hyperperistalsis followed by a transitory status of fatigue of the stomach muscle and antral dilatation. The overnight fasting gastric fluid was 500 cc., with high acidity. The patient was operated on two weeks after the hematemesis. A pyloric ulcer located in the pyloric canal with exteriorization and penetration into the pancreas was found. A subtotal gastrectomy was performed (Hofmeister-Polya with retro colic gastro jejunostomy). The histological examination showed a benign lesion. (Fig. 3)

Comments: This is a case in which existed a typical intermittent evolution of a peptic ulcer with no changes in the character and rhythm of the disease for more than 15 years. In 1950, a progressive virulence of signs and symptoms was observed which brought the patient to surgery.

Case No. 2—(No. 41778)

M. R. 59 year old female. Was operated on in 1934 for a spinal cord tumor (meningioma) at the 7th thoracic segment (Mount Sinai Hospital). She was in fairly good condition until the middle of 1945 when she complained again of stiffness of lower extremities and loss of balance. A pantopaque myelogram showed an obstruction at the level of the upper border of the 11th thoracic vertebra. A leminectomy was performed on March 19, 1946, which showed dense arachnoidal adhesions at site of previous operation. A course of radiotherapy was given subsequently at Montefiore Hospital. The first gastric symptoms appeared in October, 1946, when the patient had a 3 weeks episode of epigastric pain after meals. Then, for several weeks, there were no digestive complaints. Another attack of 3 weeks duration occurred after this remission; thereafter, a succession of epigastric attacks and recoveries occurred, the patient began having 2 to 3 attacks of 2-3 weeks duration every year. In 1946 a niche was found in the vertical part of the lesser curvature on x-rays. The same examination repeated in 1947 during a free interval failed to show the niche or any other abnormality. In May 1950, a severe attack occurred coinciding with another series of radiotherapy. The epigastric pains were very acute, relapsed for a short time, recurred, and, at that time, were accompanied by marked abdominal distention and paretic status of the digestive tract, which was confirmed by x-rays.

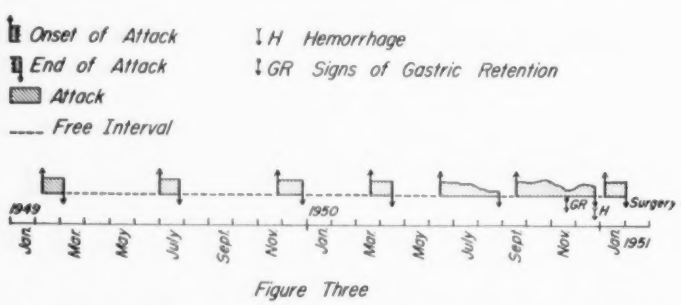

Figure Three

Case No. 1.—Typical periodical evolution of an ulcer for 15 years. In 1950 started a progressive virulence, with signs of gastric retention and hemorrhages.

Comment: This case is similar to Case No. 1. Progressive virulence occurred after a relatively long evolution of a periodical, non-progressive disease. The severe reactivation of the ulcer seems, in this case, to have coincided with the radiotherapy administered for the sequellae of a surgically removed spinal cord tumor. When the disease became virulent the patient repeatedly vomited undigested food and, on July 10th, had a hematemesis which was followed by partial remission of symptoms. In September 1950, x-rays showed aspects which were interpreted as corresponding to a polypoid carcinoma of proximal two thirds of the stomach with an area of deep ulceration on the lesser curvature in the region of the cardia. The impression was of an extensive carcinomatosis of the stomach. There was, however, some doubt of the correctness of the diagnosis. The patient had a long history of a typical periodical evolution of a benign ulcer. The x-rays had shown a niche appearing and disappearing with the fluctuations of the disease. In addition mucosal fold studies showed that the lacunar radiological aspects seen in the last x-rays of 1950 could be interpreted as hypertrophic rugae around an ulcer niche. The probability of a benign ulcer was finally strongly suggested, although the gastric acidity was low. Surgical exploration showed a localized infiltration in the middle of the lesser curvature of the stomach. A large gastrectomy was performed. It was only after examination of the gross and microscopic specimen that the benign nature of the lesion was confirmed, explaining the chronic, long, intermittent evolution, the absence of permanent deformities on x-ray and justifying the interpretation of the pseudo lacunar aspects as hypertrophic rugae. (Fig. 4).

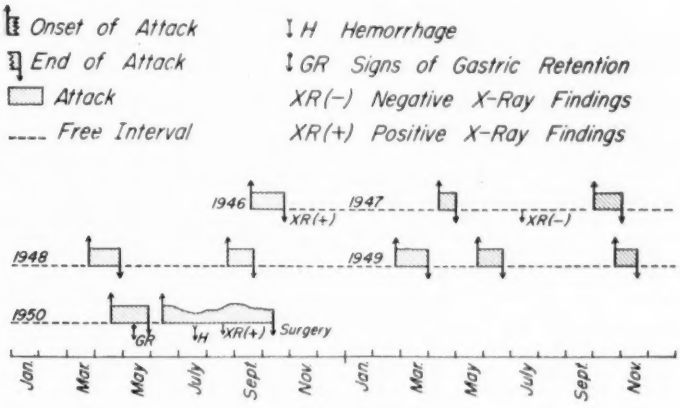

Figure Four

Case No. 2.—Similar to Case No. 1. At the time of progressive virulence the signs and symptoms and the radiological aspects simulated a superimposed malignancy.

an erroneous diagnosis of extended carcinomatosis of the stomach was made. The histology was in accordance with the clinical and radiological data and confirmed the benign nature of the lesion.

Case No. 3.

R. C. 29 year old white male. This patient, a physician, was seen by one of us for the first time in January 1936. His disease started in 1927, at the age of 20. Since that time he was suffering attacks lasting 10-15 days of post-prandial transfixiant pain with free intervals of 2-3 months. The diagnosis of a typical edematous duodenal ulcer was made by x-ray in 1930. At the time of our first examination the radiological signs were still present. No appreciable other abnormalities were found. Physical examination was negative. The gastric acidity was slightly elevated. No occult blood was found in the stools. The patient appeared as a well nourished man. At that time he was temporarily out of practice following post-graduate courses. Because of these conditions which gave him a certain freedom of time, the patient himself decided to follow a prolonged Sippy diet and ulcer treatment. For one year he confined himself to a very strict regime, olive oil, milk, fruits, and took alkalies, bismuth and vitamins. During that year he had the same sequence of attacks and recoveries that he had before, when he was following no specific diet. The attacks, however, were shortened and the pain less intense; the x-ray picture during these attacks remained unchanged. Considering that this was a poor result in view of the strenuous treatment he had followed; considering also the weight loss, diminishing strength and the existence of a high blood calcium (although no apparent renal disorder was noted), he decided to return to his former modus vivendi. (Fig. 5).

Comment: This is an example of the lack of influence of a prolonged and very strict diet and medication on the rhythm of evolution of an uncomplicated peptic ulcer.

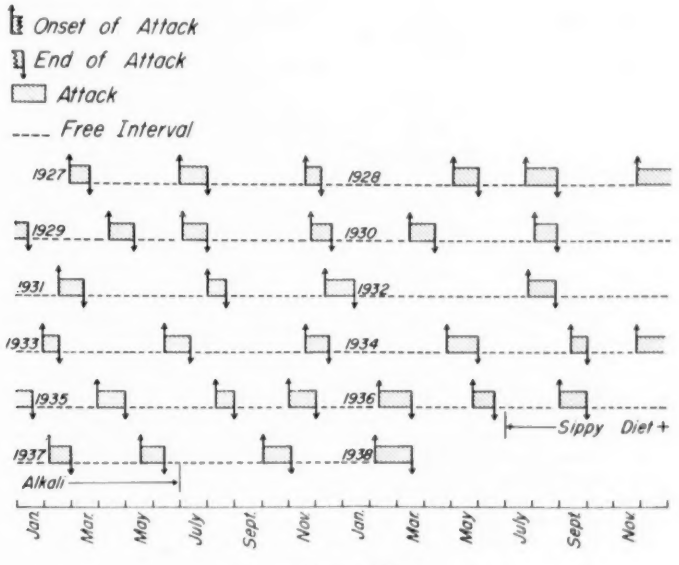

Figure Five

Case No. 3.—Typical non progressive evolution of a benign ulcer in which a prolonged Sippy diet and alkaline medication left unchanged the rhythm of periodicity.

Case No. 4.

G. L. 34 year old white male. The disease started in 1930. From 1930 to 1933 the patient had one or two attacks every year, lasting several days, of acute epigastric pain after meals. At several of these attacks a marked melena was observed which shortened the attack. A diagnosis of duodenal ulcer was made on x-rays in 1933, and, because of the intensity of pains and repeated bleedings an operation was decided upon. At the operation, performed during a free interval, no ulceration was found, the diagnosis of peptic ulcer denied and a cholecystectomy was performed for an unknown reason. After this first operation, and for 10 years, the patient had one or two attacks a year, most of the time consisting of massive hemetamesis and melena; some attacks, however, were painful and not accompanied by bleeding. The diagnosis of duodenal ulcer was again established by x-rays, and the patient was re-operated on in 1942. The ulcer, at that time, was recognized in the midst of multiple adhesions due to the former cholecystectomy. No resection of the bleeding ulcer was possible. A gastrectomy was performed. Following this second operation, and for almost 5 years, the patient was free of symptoms. These recurred at the beginning of 1947. When we saw the patient, for the first time, in February 1947, he was convalescing from a severe attack of excruciating post-prandial pain which was interpreted as possibly due to a marginal post-operative ulcer. Our examination failed to reveal any abnormality of the anastomotic region. A definite niche was visible in the duodenal stump retrogradely filled through the afferent loop. This niche surrounded by edematous aspects, was located at a half inch of the duodenal section and was interpreted as representing the primary ulcer still active. After various consultations, a new surgical intervention was refused because of considerable technical risks. Since 1947, we have seen the patient regularly. He has had, once or twice a year, either massive gastro-intestinal bleedings or episodes of post-prandial pains. The bleeding episodes have been invariably dramatic, almost exsanguinating the patient. The last episode of bleeding occurred in February 1952, when the patient was in Florida, and, after partial control of the hemorrhage, the patient was brought back to New York by plane ambulance. At the time this was written (July 1952) no solution has been found to this difficult problem. Vagotomy is discussed. (Fig. 6).

Comment: In this case of a bleeding ulcer with frequent hemorrhagic "equivalents," the duodenal lesion was not found at the first operation, performed during a free interval; the diagnosis of duodenal ulcer was denied, symptoms were erroneously reported to be a cholecystitis and a cholecystectomy was performed. That undoubtedly increased the technical difficulties at the second operation and the situation, since, has remained difficult to control.

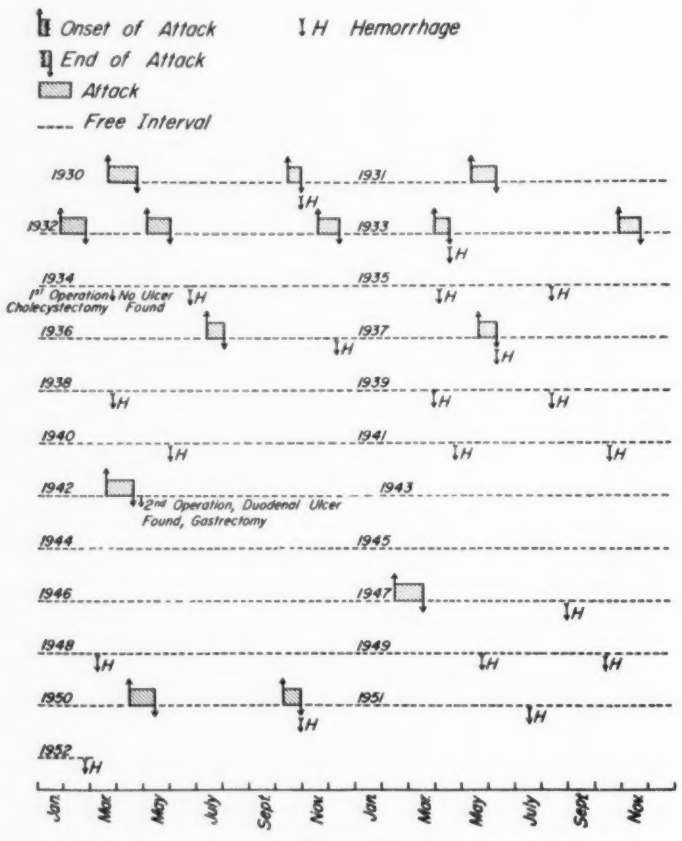

Figure Six

Case No. 4.—Bleeding ulcer with frequent hemorrhagic "equivalents." The ulcer was not found at a first operation performed during a free interval of the disease. A second laparotomy, performed near the end of an active episode, showed the lesion. The ulcer, however, could not be removed and remained active after subtotal gastrectomy.

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OBESITY: OVERNUTRITION OR DISEASE OF METABOLISM?

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ALTHOUGH IT IS widely believed that physiological experiments have proven the absence of any metabolic defect in the etiology of obesity, a clear-cut analysis of the manner in which they are presumed to have done so is difficult to find. Discussions of the subject often emphasize that the energy intake must exceed the expenditure when obesity is developing: but this elementary knowledge, deducible from the law of conservation of energy, needs no experiment. The question on which an experimental answer has been sought is whether the positive caloric balance associated with obesity arises from causes extrinsic to the metabolism or from some intrinsic metabolic defect.

Many experiments have failed to reveal any metabolic alteration from the normal in obesity. Basal metabolism tests have ruled out disease of the thyroid gland; and many explorations of the intermediary metabolism have given negative results. Since, however, these do not rule out the possibility of some still undiscovered defect, studies of the energy exchange have attempted to answer the essential question whether or not a metabolic aberration can, at all, account for obesity.

Studies of the energy exchange might well be expected to answer this crucial question by showing whether the excessive energy storage of the obese is causally dependent on the balance between energy intake and expenditure or if it maintains a significant degree of independence of that balance. In either case, the necessities of the energy equation,

energy intake = energy storage + energy expenditure,

must be fulfilled. In this equation, energy storage may be positive or negative in sign. Experimental investigation of the matter has been attempted by altering the energy intake and observing the effect of this on energy storage and expenditure. If the excessive energy stores of the obese depend passively on the balance between energy intake and expenditure, caloric restriction should be followed by utilization of stored energy in an amount equivalent to the calorie deficit of the diet, with no more decline in energy expenditure than would be anticipated from the reduction in body weight. If, on the other hand, the excessive energy stores arise from some intrinsic metabolic aberration, they would be expected to show a significant degree of independence of the balance between energy intake and energy expenditure; caloric restriction, in such a case, would not be followed by utilization of stored energy in an amount equivalent to the calorie deficit of the diet, and the energy expenditure would show a significant decline.

Control Studies on Normal Individuals

Two types of energy balance studies on normal individuals serve as controls for studies on the obese. In one type, individuals of normal weight have been subjected to subcaloric diets; and in the other, normal-weight individuals have first increased their weight by purposeful overfeeding and then lowered their caloric intake. The effects of caloric restriction on metabolically normal individuals under these two circumstances form a background for evaluating the effects of caloric restriction on individuals in whom obesity has arisen, as it ordinarily does, spontaneously. Table 1 shows the effects of caloric restriction on the basal energy expenditure of individuals of normal weight subjected to undernutrition.

TABLE I

AVERAGE DECLINE IN ENERGY EXPENDITURE OF INDIVIDUALS OF NORMAL WEIGHT, DURING UNDERNUTRITION

Source	*Decline in basal calories*	*Decline in B.M.R.*
Benedict (Squad A) (1)	19 per cent	16.2 per cent
Benedict (Squad B) (1)	32 per cent	27 per cent
Taylor and Keys (2)	39 per cent	31.2 per cent

It is apparent from the table that a varying but significant decline in energy expenditure occurs when people of normal weight are subjected to subcaloric nutrition. This would indicate that the normal energy stores of the body maintain a considerable degree of independence of the energy balance. It would seem to coincide with evidence from other sources that the normal energy stores of the body are regulated by intrinsic metabolic mechanisms (3). They are not yielded for energy in an amount equivalent to the calorie deficit of a subcaloric diet and, as a result, there is seen the "specific reduction in metabolism coincident with undernutrition" (4).

Table 2 shows the effects of reduction in the caloric intake on the basal energy expenditure of two normal individuals who first increased their weight by purposeful overfeeding.

TABLE II

EFFECTS ON THE BASAL METABOLIC RATE OF PURPOSEFUL OVERFEEDING AND SUBSEQUENT CALORIC RESTRICTION IN NORMAL INDIVIDUALS

Source	*B.M.R. before overfeeding*	*B.M.R. after overfeeding*	*B.M.R. during caloric restriction*	*Decline from highest level*	*Decline from original level*
Gulick (5)	0%	0%	0%	0%	0%
Wiley & Newburgh (6)	−10%	−4.1%	−11.3%	7.2%	1.3%

In Gulick's case, which showed a remarkable steadiness of the metabolic rate, there was a weight gain of

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26 pounds during the course of 11 months before caloric restriction. In the case of Wiley and Newburgh there was a weight gain of 9.7 pounds during 2 weeks of very intensive overfeeding before the reduction in caloric intake. The rise and fall in basal metabolism in this case may reasonably be attributed to the temporary increase in metabolism representing energy utilized in the metabolic work of adding flesh to the body; during the rapid fattening of steers the basal metabolism may rise as much as 36 per cent (7). The more prolonged experiment of Gulick would seem to have eliminated this temporary effect by allowing time for a levelling off of the weight at the higher level. The evidence from these experiments would seem to indicate that, in metabolically normal individuals who have increased their weight by purposeful overfeeding, the excessive energy stores are passively dependent on the balance between energy intake and expenditure; for these stores respond to caloric restriction by yielding their substance for energy in an amount equivalent to the calorie deficit of the diet, with the result that no significant decline in energy expenditure occurs. Although the normal energy stores of these subjects were presumably maintained by the same intrinsic mechanisms which operate in other normal individuals, their excess stores were obviously dependent on causes extrinsic to the metabolism. These individuals, when allowing the appetite to regulate the food intake, maintained constant weight at a normal level.

STUDIES OF THE ENERGY EXCHANGE IN OBESITY

If the excessive energy stores in common obesity, which ordinarily arise spontaneously, show a passive dependence on the energy balance, as do the excessive stores of normal individuals in purposeful overfeeding experiments, their maintenance must be attributed to causes extrinsic to the metabolism, and the cause of obesity must be simple overfeeding. If, on the other hand, the excessive energy stores of the obese show a significant degree of independence of the energy balance, as do the normal energy stores of the body, their maintenance must be attributed to an intrinsic mechanism, and the cause of obesity must be a metabolic aberration involving the regulation of fat storage.

Experiments showing the effects of caloric restriction on the obese have been of two types. In one, efforts have been made to determine the amount of body substance oxidized; and in the other, efforts have been made to determine whether or not there has been a decline in the energy expenditure. Since oxidation of body substance offsets a decline in the energy expenditure, the two quantities are inversely related.

In Newburgh's studies (8), diets with a known calorie deficit were given to the obese; and, on the assumption that body fat contains 10 per cent water, the caloric value of body substance oxidized was calculated from the weight loss. It appeared from the calculations that the calorie deficit of the diet was completely compensated for by utilization of stored energy, and the conclusion was drawn that the energy expenditure remained constant. These results seemed to show that the excessive energy stores of the obese are passively dependent on changes in the energy balance and that "obesity is invariably the result of a disproportion between the inflow and the outflow of energy." Since, however, the experiments were not checked by actual determinations of the energy expenditure after caloric restriction, the results would appear to depend entirely on the value assumed for the water content of body fat. Lauter had determined this to be 10 per cent, but Bischoff had found it to be 29 per cent, Bozenraad 7 to 46 per cent, and Bozenraad had quoted others who found it to vary between 15 and 30 per cent (9). If the water content of body fat is higher than Newburgh supposed, a smaller quantity of stored energy must have been yielded by the fatty deposits than would be indicated by his calculations from the weight loss. In view of the uncertainty concerning the water content of body fat, it seems that no conclusions concerning the nature of obesity can be drawn from Newburgh's studies of the energy exchange.

Actual determinations of the energy expenditure of the obese after caloric restriction have shown that there is a significant decline. Table 3 gives the basic data from sources frequently referred to.

TABLE III

AVERAGE DECLINE IN ENERGY EXPENDITURE OF OBESE ADULTS ON LOW CALORIE DIETS

Source	*Decline in Basal Calories*	*Decline in B.M.R.*
Strang and Evans (10)	14 per cent	
Brown and Ohlson (11)	17 per cent	
Lyon and Dunlop (9)		13 per cent
Keeton and Bone (12)		12.2 per cent (calculated from graph)
Moller (13)		12.5 per cent (calculated from graph)

In children, according to tables furnished by Mulier and Topper (14), the decline in B.M.R. is less, but the authors point out that the pelidisi of Pirquet is a better measure of energy expenditure in children than is the usual surface area rule. The evidence from the basic data of all of the investigators would seem to indicate that, in the adult obese individual, caloric restriction is followed by a significant decline in energy expenditure, for the decline is greater than the decline in either the weight or the surface area (9) (15).

EVALUATION OF THE RESULTS

The decline in energy expenditure of the obese during caloric restriction, though less than that of people of normal weight during subcaloric nutrition, stands in striking contrast to the lack of decline in the metabolism of normal individuals who have first increased their weight by purposeful overfeeding and then lowered the caloric intake. It would seem from these results that, although the excessive energy stores of the obese are yielded for energy in response to a negative energy balance more readily than are the normal energy stores of the body, they, nevertheless, show a significant degree of independence of the energy balance. They do not yield their substance for energy in an amount equivalent to the calorie deficit of the diet. The excessive energy stores of the obese, there-

fore, appear to resemble the normal stores in being maintained by intrinsic metabolic mechanisms. The evidence would appear to indicate that energy storage in the obese is regulated very much as it is in people of normal weight, but at an abnormally high level. This would seem to necessitate an explanation of obesity as due to some metabolic aberration involving the regulation of fat storage.

These generalizations concerning obesity are based on the averages found in the various studies. While there appears to be a considerable degree of uniformity in the averages derived from the basic data of the various investigators, a considerable range is seen among individuals within a particular study. Strang and Evans (10) for example, found declines ranging from 4 to 23 per cent in the basal caloric expenditure of the obese on low calorie diets. In Benedict's Squad A of individuals of normal weight, the decline in basal caloric expenditure during subcaloric nutrition was not far different, ranging from 9.5 to 26.6 per cent (16). There appear to be wide variations in the response of both normal-weight and obese individuals to subcaloric nutrition, some of each group showing a greater resistance to a negative caloric balance than others.

The variations among the obese might be explained in the following ways. In some of the subjects who display a considerable lability of the energy stores, the metabolism may be relatively normal, and the excess weight may be due largely to purposeful overfeeding, chiefly of carbohydrates, as it is in metabolically normal individuals who have subjected themselves to overnutrition experiments. On the other hand, the relative lability of the energy stores might be accounted for by an incipient failure of the fat storage mechanism, which would come to full realization in the diabetic state. In those obese subjects whose energy stores show a considerable resistance or stability, some metabolic aberration involving fat storage would be the most reasonable inference. The evidence, in any case, does not seem to support the extreme view that obesity is invariably due to simple overfeeding.

OBJECTIONS TO THE EVIDENCE

Although it would seem that energy balance studies have given valid evidence for some explanation other than simple overfeeding in a considerable proportion of obese subjects, there appears to have been some hesitancy in accepting this evidence, even by some of the investigators themselves. This body of evidence and its significance have been assailed in many various ways.

Strang and Evans (10) introduced a novel method of calculating metabolic rates of the obese, based on the ideal, rather than the actual weight. This caused the metabolism of the obese to appear hypernormal, and tended to minimize the significance of the actual decline in energy expenditure. The method was based on the assumption that adipose tissue is metabolically inactive and that its weight, therefore, should not be taken into account when metabolic calculations are made. The discovery that adipose tissue is metabolically active (3), however, would appear to rule out the validity of metabolic calculations based on ideal weights.

Keeton and Bone (12), in interpreting their results, assumed that a decline in energy expenditure is not significant as long as the metabolic rate does not fall below the limit of minus 10 per cent, which is widely accepted for clinical diagnostic purposes as the arbitrary low limit of normal. In physiological experiments, however, the significance of the results depends on measurements of the actual changes in variable quantities. Moller interpreted his one case in the same manner as Keeton and Bone.

Rynearson (17) in discussing the decline in energy expenditure, which he concedes is of some importance, points out that different investigators have found different results. Examination of the basic data of the various investigators, however, shows a remarkable uniformity of results and a difference only in some of their conclusions. In Moller's one case, there was a temporary though significant rise in the metabolism at the 19th week, coincident with a levelling off of the weight reduction curve which, according to the author's explanation, would indicate a departure from the diet at this time. It would seem that a decline in metabolism persists when dietary restrictions are adhered to.

ADJUSTMENTS IN THE ENERGY BALANCE SECONDARY TO PRIMARY ALTERATION IN ENERGY STORAGE

The basic data of those who have investigated the energy exchange in obesity would seem to indicate that, in a considerable number of cases, this condition arises from an intrinsic aberration in the regulation of energy storage. Certain results must, of necessity, follow from this; for it is evident from the energy equation, energy intake = energy storage + energy expenditure, that a primary increase in energy storage must be compensated for either by an increase in the energy intake or by a decrease in the energy expenditure. The forces influencing an increased energy intake would be felt subjectively as an increase in appetite but, if food is restricted, the adjustment in the energy equation must take place in the only way possible: through a decrease in the energy expenditure.

A primary increase in fat storage, with these secondary effects, has been found by Brooks in animal experiments. Some of his animals with obesity-producing lesions in the hypothalamus gained more weight than the normal controls, though the food intake was kept the same (18). As long as the food intake was kept at normal the basal caloric expenditure remained below normal (19). The animals readily ingested more food when it was provided, and their basal caloric expenditure then rose. They rapidly became obese, however, for the increase in energy expenditure did not keep pace with the increase in energy intake. The weight of such animals can be brought to normal by severe caloric restriction, but it invariably rises to a high level again when food restrictions are removed

Similar circumstances in common obesity in humans are indicated by the studies of Brown and Ohlson (11). Their obese subjects, after reducing, maintained their weight at a normal level by means of caloric restriction, but at the expense of a subnormal basal caloric expenditure. They maintained normal weight on a food

intake lower than that of other people of the same age and dimensions; and they characteristically experienced hunger. It would appear that when obese people reduce their weight by caloric restriction, the intrinsic metabolic aberration promoting excessive fat storage is still operative, producing an urge to increase the food intake and, if this is restricted, a decline in the basal metabolism.

SIGNIFICANCE OF A LOWERED BASAL METABOLISM

In view of the hazards of the obese state, it might seem that the formerly obese individual might well afford to endure hunger and to accept the lowered basal metabolism as an inconsequential matter. It seems, however, that the significance of a lowered basal metabolism has been obscured by the wide normal range allowed for clinical diagnostic purposes. DuBois states that the basal metabolism test has been useful chiefly in the diagnosis of disease of the thyroid gland (20). As long as the basal metabolism stays within the limits which usually exclude a diagnosis of thyroid disease, further thought of it is usually abandoned, perhaps on the ground that enough heat is being produced to keep the body warm. A more widely applicable significance of the basal metabolism was indicated by Benedict, who considered it to be a "very good index of the general state or level of vital activities" (21). The basal caloric expenditure represents the amount of metabolic work being accomplished by the body; and heat and to spare is ordinarily given off as an end product, very much as water over a dam runs downstream after turning the machinery of a mill. A decline in the basal energy expenditure following a decline in the food intake must be attributed to a decline in the amount of nutriment which the organism is able to convert into types of energy necessary for its vital activities. A great part of the basal energy expenditure represents energy utilized by the liver; and it seems that the basal energy expenditure must reflect, in large measure, the level of caloric nutrition in this organ. In view of the caloric needs of the liver for repair and for prevention of damage (22), a prolonged calorie shortage here, in many patients, can not be regarded lightly. Actually, there is hardly any evidence that caloric restriction produces, in the long run, the benefits which the obese are often led to expect (23).

TREATMENT OF OBESITY

There is no doubt that obesity constitutes a clinical problem of the highest importance; but, in many cases, treatment by caloric restriction does not appear to be a very satisfactory solution. It would seem that a rational treatment of obesity should be based on measures which take into account the pathologic physiology of this condition and which avoid a decline in the basal energy expenditure.

During the past half-century many investigators have opposed the concept of obesity as due to simple overnutrition; and a number of studies of the intermediary metabolism have, in fact, revealed variations from the normal in the obese (24, 25, 26). Work in this field has advanced rapidly since the introduction of isotopes in biochemical experiments (27); and it appears that the question of the specific nature of the intrinsic metabolic fault leading to excessive fat storage will soon be, if it is not already, clarified. There appears reason to believe that it is an enzyme block in the breakdown of carbohydrate at the pyruvic acid level. As a result of this block, it seems, much of the carbohydrate ordinarily ingested is converted to fat, while the presence of excess pyruvic acid in the tissues hinders the oxidation of fat (28).

If obesity can be caused in this way, restriction of carbohydrate, specifically, in the diet should make ineffective the metabolic aberration which promotes and maintains excessive fat storage, for there would be less pyruvic acid formed. The excessive energy stores should then yield their substance for energy, causing energy storage to become negative in sign in the energy equation,

energy intake = energy storage + energy expenditure.

The energy equation would then, of necessity, come into balance through an increase in the energy expenditure or a decrease in the energy intake, or both; and the normal relation of the food intake to energy needs (29) would be expected to allow for effective weight loss, with the intake of the non-carbohydrate elements of the diet, protein and fat, regulated entirely by the appetite.

An experiment which appears to have demonstrated this was performed at the Russell Sage Institute in 1928 (30, 31). Three subjects lost some weight on an *ad libitum* intake of lean and fat meat and they all showed an increase in the caloric expenditure during the period of weight loss. Table 4 shows these results.

TABLE IV

LOSS OF WEIGHT, WITH INCREASE IN THE ENERGY EXPENDITURE ON AN AD LIBITUM INTAKE OF PROTEIN AND FAT

Subject	*Loss of weight (kilograms)*	*Increase in basal calories*	*Increase in B. M. R.*
V. S.	4.2	8.9 per cent	7 per cent
K. A.	.9	16 per cent	5 per cent
E. F. D. B.	2.8		6 per cent

None of these subjects was very much overweight. The weight loss occurred during the first month on the diet; and two of the subjects, who then continued on the diet for a full year without any ill effects from it, maintained a relatively constant weight level. It appeared that, on this diet, in which the subjects derived, by choice, about 80 per cent of the calories from fat, 1 to 2 per cent from carbohydrate, and the rest from protein, the excess fatty deposits of the body were utilized for energy but the normal energy stores were maintained.

The proportions of protein and fat in the diet would be represented by three parts of lean meat to one part of fat, by weight. A small amount of carbohydrate is present as the glycogen of the meat. The subjects of the experiment ingested food to the amount of 2000 to 3100 calories a day, the precise amounts depending upon their appetites. In round figures this would be represented by 2 to 3 ounces of fat and 6 to 9 ounces of lean meat at each of the three meals of the day.

This diet, with some modifications, has formed the basis of a treatment of obesity which has been used in clinical practice for more than two decades (32). During the past few years it has been used in a group of industrially employed individuals (33, 34); and it appears to have many advantages over treatment by caloric restriction. It seems that it would be useful, especially, in those cases of obesity in which the application of low calorie diets results in hunger or in a decline in the energy expenditure.

SUMMARY

Analysis of the results of studies of the energy exchange in obesity, in regard to their evidence for or against a passive dependence of the excessive energy stores on the balance between the inflow and the outflow of energy, indicates that these stores have a significant degree of independence of the energy balance. This appears to necessitate an explanation of obesity on the basis of some intrinsic metabolic defect. The decline in energy expenditure which occurs when the obese go on low calorie diets appears to have the same significance as it has when people of normal weight are subjected to undernutrition. A treatment of obesity, alternate to that of caloric restriction, takes into account the metabolic defect in obesity, aims at a primary decrease in the excessive energy stores, and allows for weight reduction without any decline in the energy expenditure and without any enforcement of caloric restriction.

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APPENDIX

References and Notes, in connection with paper, OBESITY: OVERNUTRITION OR METABOLIC DISEASE? by A. W. Pennington.

Reference 8. Newburgh, L. H. Obesity; In Joliffe, N., Tisdall, F. F. and Cannon, Paul R.: Clinical Nutrition, New York. Hoeber. 1950.

In this article, Newburgh summarizes his work on the energy exchange, most of which was done around 1930. The matters he takes up do not follow one another in a logical sequence but, rather, tend to carry the reader away from points on which concrete conclusions are expected.

It is clear, however, that he obtained his results from measuring the weight loss and calculating the caloric equivalent of tissue oxidized, rather than making direct determinations of the energy expenditure. For example:

Page 697: "Under these circumstances, change in body weight could be attributed to deposition or loss of adipose tissue, provided the observations of any subject were continued for several weeks. When the record was completed the average daily metabolic mixture would correspond with the diet except that any change in body weight over the whole period would have to be reduced to a daily average and then 90 per cent of it either added to or substracted from the dietary fat. (Since adipose tissue contains 10 per cent body water and dietary fat is expressed in anhydrous terms, 90 per cent of the weight is used.) *The calories of the diet, thus corrected, were taken to be the daily heat production of the subject.*"

The reader becomes impressed with the correctness of the predictions of weight loss; but these could be made on the basis of empirical observations during weight reduction, regardless of the water content of the body fat and of the caloric equivalent of tissue oxidized for energy. Thus, without a check by actual determinations of the caloric expenditure during weight reduction, the results obtained depend entirely on the assumption of a 10 percent water content in body fat.

Page 720: ". . . the simple principle will remain that obesity is invariably the result of a disproportion between the inflow and the outflow of energy. The former must always be greater than the latter, either because the intake has increased or the outgo has diminished." Thus, in summarizing, Newburgh gives data deducible from the law of conservation of energy and requiring no experiment; but to it he adds the implication that the entire pathogenesis of obesity can be summed up in this way. His statement would seem to indicate that the excessive stores of the obese are *passively dependent* on the disproportion between the inflow and the outflow of energy. His experiments did not prove this, however, for they were based on the assumption concerning the water content of body fat.

It is only after a very painstaking study of this article and of Newburgh's earlier papers that it becomes clear as to exactly what he was trying to find out in his experiments, how he proceeded to find out and what his results were. Many of my colleagues tell me, "Newburgh has done a lot of work on the matter," but no one seems to know exactly what he did, or did not do.

Reference 10: Evans, F. A.: Obesity, In Diseases of Metabolism, ed. 2, by Duncan, G. Phila. Saunders. 1947.

Table 14, page 545, gives the observed basal calories before and after weight reduction, in cases 1 to 5. These are listed in the first two columns below. In the third column are my calculations of the percentage decline.

Case No.	Observed basal calories before reduction	Observed basal calories after weight reduction	Calculated per cent decline
1.	69	53	23
2.	70	61	13
3.	72	69	4
4.	74	62	16
5.	70	60	14
Average	71	61	14

Note the wide range of 4 to 23 percent in the decline in basal calories.

Reference 11: Brown, E. G. and Ohlson, M. A.: Weight reduction of obese women of college age. Clinical results and basal metabolism. J. Am. Diet. A. 22: 849, 1946.

Basal calories per 24 hours:	Averages
Before weight reduction	1421
During diet period	1175
Post reduction maintenance	1216
Mean for Iowa State College Women	1368

Reference 12: Keeton, R. W. and Bone, D. D.: Diets low in calories containing varying amounts of fat. Their effect on loss in weight and on the metabolic rate in obese patients. Arch. Int. Med. 55:262-270, 1935.

The authors say they found no decline in metabolism. From their graphs of basal metabolic rates, however, we find the following:

Case	B. M. R. at beginning	B. M. R. at end	Change in B. M. R.
M. H.	+10	+10	0
H. H.	-2	-11	-9
L. M.	+4	-2	-6
S. C.	0	+1	+1
M. M.	+10	-1	-11
H. K.	+36	+8	-28
N. P.	+10	-1	-11
N. P.	+10	0	-10
		average	-12.2

Note: There was a decline in metabolism in all but two of the cases.

Reference 13: Moller, Eggert: Results of exclusively dietary treatment in 46 cases of obesity. Acta Med. Scandinav. 74:341, 1931.

The author reports on the metabolism in only one

case, that of subject J. R. (Figure 3). Calculation from the graph of this case shows the following:

B. M. R. at beginning of diet period	+2.5 per cent
B. M. R. at end of diet period	−10 per cent
Decline in B. M. R.	12.5 per cent

It is noted that there was a steady decline in B. M. R. during the first three weeks of dieting. Then there were variations in the metabolism curve. It will be seen that these variations coincide, quite accurately, with temporary levellings of the weight reduction curve. In the text, the author attributes such levellings to departures from the diet, some of which were known and others inferred from the effects on the weight curve when departures from the diet were definitely known, such as at Christmas time.

Reference 14: Mulier, H. and Topper, A.: Treatment of obesity in a group of children. Am. J. Dis. Child. 47:25-33 (Jan.) 1934.

Although the authors state that there was no reduction in basal metabolic rate, calculations from their tables show an average decline of 2.8 per cent in boys and 4.8 per cent in girls.

Reference 16: Benedict, F. G., Miles, W. R., Roth, P., and Smith, H. M.: Human vitality and efficiency under prolonged restricted diet Carnegie Institution of Washington Pub. No. 280, 1919.

Page 513, Table 128. Basal calories per 24 hours are given before and after dieting. From these, I have calculated, in the third column, the decline in basal calories and, in the fourth column, the percentage decline:

Subject	Basal calories on normal diet	Basal calories at end of diet	Decline in basal cal.	Per cent decline
Bro	1481	1271	210	14.2
Cau	1758	1590	168	9.6
Kon	1818	1429	389	21.4
Gar	1815	1450	365	20.1
Gul	1698	1427	271	16.0
Mon	1858	1544	314	16.9
Moy	1638	1331	307	18.7
Pea	1766	1295	471	26.6
Pee	1589	1217	372	23
Tom	1526	1217	309	20.2
Vea	1604	1264	340	21.2
Averages	1686	1367	319	19

Note the variation in per cent decline: from 9.6 to 26.6. Note that only one of the cases showed a decline greater than 23 per cent, which was shown by Strang and Evans in their obese subject No. 1.

Reference 17: Rynearson, E. H. and Gastineau, C. F.: Obesity. Springfield. C. C. Thomas. 1949.

Page 18. Here he discusses the decline in metabolism of the obese on low calorie diets. In my paper I have given the basic data from all of the papers he has referred to. He referred to Rony's book, Obesity and Leanness, but Rony used the material from Strang and Evans and from Keeton and Bone.

Reference 30: McClellan, W. S. and DuBois, E. F.: Prolonged meat diets with a study of kidney function and ketosis. J. Biol. Chem. 87: 651, 1930.

Effects of the diet on the weight:

Subject	Start of diet (Kg)	End of one week	End of one month	End of year
V. S.	72.2	70.2	68	69.4
K. A.	59.4	58.3	58.5	58
E. F. D. B.	76.0	73.2		

Reference 31: McClellan, W. S. Spencer, H. J. and Falk, E. A.: Prolonged meat diets with a study of the respiratory metabolism. J. Biol. Chem. 93:419, 1931.

Effects of the diet on caloric expenditure (per hour):

Basal metabolism of V. S.		Basal metabolism of K. A.	
2/2/28 mixed diet	60.96	1/10/28 mixed diet	52.35
4/12/28 meat	66.38	1/31-4/13/28 meat	60.71

"After meat was taken for 6 weeks the B.M.R. of V. S. was 7 per cent above that found in the period of mixed diet and similarly the rate of K. A. rose 5%." It is also stated that the rate of E. F. D. B. rose 6%. He stayed on the diet only 2 weeks. It did not disagree with him but he felt unhappy about it or had qualms about it.

THE ALPHA CELLS OF PANCREATIC ISLETS AND THE PATHOGENESIS OF DIABETES MELLITUS

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THE PAINSTAKING work of the experimentalist and the clinician initiated by Minkowski's classical production of diabetes through pancreatectomy has firmly established the central position of islets of Langerhans in the etiology of diabetes. However, we still do not know what constitutes the anatomo-pathological substrate of this disease and remain puzzled by the paucity or even absence of any demonstrable pancreatic lesions in many cases of diabetes.

Hyalinization of islets, long assumed to represent a typical pathological change in the diabetic, was found by Bell in only 40 per cent of diabetic islets (1). It is seen predominantly in middle or late life, and recently has been shown to result from deposition of amyloid or of an amyloid-like substance (2). It can hardly be viewed as evidence of insular inability to secrete insulin since it occurs in absence of diabetes (2, 3) as well as in functioning islet adenoma (4).

The concept that in response to functional overstimulation the beta cells undergo hydropic vacuolation indicative of islet damage was weakened by Warren's observations that these may be post-mortem changes (2) and the demonstration by Duff and Toreson (5) that in alloxanized rabbits given small amounts of insulin, hydropic changes fail to develop in spite of persistent hyperglycemia. The pathogenic significance of hydropic vacuolation of beta cells was particularly put in doubt by Toreson's finding of glycogen deposition in such cells (6).

A notable contribution to the study of islet histology was the introduction of phase contrast microscopy by Hartroft (7). In islets from diabetic patients which were free from hyalinization or fibrosis, he observed reduplication of the capillary base membrane which he interpreted as an early stage of hyalinization. The significance of this lesion was enhanced by evidence that it was associated with a marked increase in the size of beta granules. From this Hartroft concluded that the membrane may interfere with release of insulin from the cells and so decrease their secretory activity. However, he did not consider the reduplication of the membrane as pathognomonic for diabetes since he found it in a few nondiabetics and could not demonstrate it in 11 per cent of diabetics of his series.

Inasmuch as insulin is secreted by the islet beta cells it was thought that studies of the islet mass or volume or of the islet count could yield valuable information on the anatomic substrate of diabetes. Such quantitative studies of the insular apparatus are, however, handicapped by the great variability in the size of islets and the difficulty in measuring accurately the islet mass or carrying out a complete islet count. Important, too, in this connection is the fact that as little as 1/8 of pancreatic tissue left in situ is sufficient protection against the development of diabetes by pancreatectomy.

Another concept of pathologic criteria of diabetes stems from two recent developments. One is the identification in pancreatic extracts of a hyperglycemic substance, and the other the introduction of staining technics which make it possible to differentiate clearly the alpha and the beta cells.

Shortly after the discovery of insulin it was noted that, except for the Danish insulin Novo, all other insulin preparations produced an initial rise in the blood sugar of small magnitude and short duration. The substance responsible for this hyperglycemia was termed glucagon by Kimball and Murlin (8) and now carries the name of the hyperglycemic-glycogenolytic factor (HGF). It was recently obtained in purified form and shown to be a true hormone (9).

Earlier work has strongly suggested that the factor raises the blood sugar by stimulating hepatic glycogenolysis (10-15) and this has been conclusively established by the brilliant investigations of Sutherland and Cori (16). Using liver slices to assay glycogenolytic activity and P^{32} to measure the ester phosphate they found that the factor, similarly to epinephrine, increased the activity of hepatic phosphorylase by accelerating the resynthesis of active phosphorylase.

That the alpha cells may be endowed with secretory activity was suggested as early as 1907 by Lane (17), but that they may secrete a hormone antagonistic to insulin became apparent from observations on the selective destruction of beta cells by alloxan. Thorogood and Zimmerman (18) having found that pancreatectomy carried out in the alloxanized dog was followed by a decrease in glycosuria and in insulin requirement, postulated the existence of a hyperglycemic pancreatic hormone, most likely secreted by the alpha cells. In cross-circulation experiments, Foá et al. (19) recorded a rise in blood sugar in a normal dog perfused with blood from the pancreaticoduodenal vein of an alloxanized donor animal; they noted a much lesser hyperglycemic response when blood from the mesenteric vein of the donor dog was used. Such observations, coupled with the work on the hyperglycemic factor, have led to the conclusion that the factor is produced in alpha cells; and it is of interest that the factor was found, besides the pancreas, in segments of the gastric and intestinal mucosa (20) in which the presence of alpha cells was also demonstrated (21).

In keeping with these facts, Ferner (21) has recently presented a new theory of diabetes. With the use of Gomori's staining technics and his own modification of the Gros-Schultze silver stain for alpha cells, this author made important contributions in the field of islet morphology. In his earlier work he concluded that alpha cells were precursors of beta cells, but now believes that no such transition occurs in islets of the adult man and assigns to alpha cells the elaboration of the hyperglycemic hormone. In his experience, alpha cells make up some 20 per cent of

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islet cells in normal adults, and 30 per cent or more in diabetic patients. Thus in diabetes he finds an increased ratio of insular alpha to beta cells (the so-called A:B ratio) and contends that the specific anatomic substrate of this disease is an increase in alpha with simultaneous decrease in beta cells. There is, in addition, hyperplasia of alpha cells outside of the islets, that is, in the ducts and the acinar tissue of the pancreas. In Ferner's opinion the immediate cause of diabetes is not an insulin insufficiency but rather insular dysfunction in which the predominance of the "glucagon system" is the decisive factor.

Conversely, in islet adenoma Ferner found the alpha cells to be decreased to such an extent as to speak of "a pure culture of beta cells." Complete or almost complete absence of alpha cells in infants with familial spontaneous hypoglycemia was also reported by McQuarrie et al. (22).

The role of alpha cells and the significance of the A:B ratio in disorders of the carbohydrate metabolism may be considered in three different areas.

First, the concept that alpha cells are the site of production of an anti-insulin hormone is difficult to reconcile with certain known facts. In the newborn, for instance, these cells make up some 40-50 per cent of islet cells, but the glucose content of the blood is lower than in the adult and actual hypoglycemia is not infrequent (23). The relatively moderate insulin requirement and the marked sensitivity to exogenous insulin after total pancreatectomy have been attributed to loss of alpha cells in this procedure. However, the altered nutritional state of the pancreatectomized animal or man may offer a simpler explanation of such observations. Thus in alloxanized dogs with superimposed pancreatectomy, Mirsky et al. (24) demonstrated a decrease in intestinal absorption of carbohydrate precursors which could account for the decreased glycosuria. When, however, such animals were subjected to fasting, their metabolic disorder was of greater magnitude than prior to surgery.

A more direct approach to the study of secretory properties of alpha cells was initiated by Van Campenhout and Cornelis (25) who discovered that these cells are selectively destroyed by cobaltous chloride. However, in guinea pigs given this compound they noted a rise in blood sugar up to 286 mg. % which they ascribed to an initial stimulation of the injured alpha cells. Goldner et al. (26) repeated these experiments in rabbits with similar results. Inasmuch as a second injection done after complete disappearance of alpha cells again produced a rise in blood sugar, a deleterious effect of the compound on extrapancreatic tissues was suggested. With the use of sodium diethyldithiocarbamate Kadota and Midorikawa (27) produced degeneration or total destruction of alpha cells associated with swelling and degranulation of beta cells. In 15 rabbits with much less selective damage to alpha cells they recorded a transient hyperglycemia which in 3 animals was followed by hypoglycemic values. Convulsions resistant to glucose developed in 2 animals, but unfortunately no blood sugar determinations were made during the convulsive seizures.

The second point to consider concerns the metabolic significance of the hyperglycemic-glycogenolytic factor. As stated before, it exerts its effect solely by stimulating the breakdown of hepatic glycogen and in consequence is without influence on the blood sugar in the hepatectomized animal or in man with depleted glycogen stores in the liver. The factor therefore cannot counteract the action of insulin in extrahepatic tissues. From the available evidence the HGF may conceivably be involved in some phases of the normal carbohydrate metabolism, but the assumption that it is a true insulin antagonist does not appear warranted.

Like the other two, the third area, that of the differential islet cell count, is one on which it is difficult to obtain unequivocal data. Thus in normal subjects the alpha cells make up from 10 to 40 per cent of islet cells according to Gomori (28) but according to other estimates they range from less than 10 per cent (29) up to 35 per cent (30), while in Hartroft's opinion (7) an A:B ratio higher than 1:3 is pathological. Disturbing, too, is Gomori's finding of a normal differential cell count in some 60 per cent of diabetic patients (31).

The thesis that disturbances in the A:B ratio are of primary etiological importance in diabetes rests on the assumption that extrapancreatic factors influence the carbohydrate metabolism through their direct effect on the pancreatic islets. That they may alter the mechanisms of insulin production and secretion cannot be doubted, but their effects outside of the pancreas must not be overlooked. This has been first demonstrated by Cori's classical work on the inhibition of the hexokinase reaction by the anterior pituitary and the adrenal cortex (32) and by Krahl's recent evidence of still another inhibitory factor of that reaction (33). No less important is Bornstein's work on the biological assay of circulating insulin. Having found zero values for plasma insulin in insulin-resistance he wisely remarked that these do not indicate absence of insulin but rather an excess of its antagonists (34).

In drawing our conclusions we may state that studies of the HGF and of islet morphology have enriched our knowledge of the carbohydrate metabolism. Alterations of the A:B ratio may well offer a pathological criterion of diabetes, particularly if taken in conjunction with reduplication of the capillary basement membrane in the islets. Nevertheless, the proof of contribution of alpha cells to the development and the progression of this disease remains in dispute.

Whatever etiological and clinical significance the alpha cells and the A:B ratio may have in disorders of the carbohydrate metabolism, such evidence must be balanced by events taking place in carbohydrate economy at the tissue level. The freshness of the reviewed data is striking and it is hoped that integrating the further work of the pathologist on islet morphology and histochemistry and that of the biochemist on the hyperglycemic hormones with our knowledge of carbohydrate transformations in peripheral tissues will give us a new overall meaning of the normal and abnormal carbohydrate metabolism

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THE EFFECT OF GASTRIC SECRETORY DEPRESSANTS (BANTHINE, BELLAFOLINE AND AMIDOPYRINE) ON THE INNERVATED GASTRIC POUCH IN DOGS

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INTRODUCTION

THE CONTINUING search for a satisfactory approach to ulcer therapy is an expression of the relative inadequacy of the methods currently in use. The recent revival of bi-vagotomy (1) first introduced 60 years ago, has again, in spite of initial enthusiasm, been found disappointing (2, 3, 5).

Atropine has long been relied upon to depress the gastric secretion and to reduce the gastric motility, but doubt regarding its efficacy has grown during the last two decades: Bastedo (6), Goodman et al. (7), Levin et al. (8), Gill et al. (9, 13), Necheles (10), Avey et al. and Zweig et al. (11, 12) among others, stress that desirable results can be obtained only with very high or toxic doses. There is ample evidence that the effect of atropine is considerably enhanced by subcutaneous and intravenous administration (12, 14). Levin and his associates point out that this enhancement is frequently associated with toxic symptoms (15).

On the whole, the data available in the literature are inconclusive, often contradictory, and do not foster confidence in the relative constancy of effects to be obtained in peptic ulcer patients with atropine administered orally. This lack of confidence is echoed in the clinical experience of most physicians, and is responsible for the keen interest in the publications of Hambourger et al. (16) Longino et al. (17) dealing with a new gastric secretory and motor depressant, Banthine. It is also perhaps not without significance that one of the moving spirits in the recently reawakened interest in vagotomy should be one of the early contributors to the literature dealing with this drug. In a recent publication, Dragstedt and his co-workers (18) expressed the opinion that it may be a useful drug in the treatment of peptic ulcer patients.

The purpose of this publication is to report our observations on the effect produced by Banthine on the gastric secretion of dogs with vagally innervated pouches, under carefully controlled conditions; to compare these effects with those obtained with Bellafoline (total levorotary alkaloids of belladonna), and with a drug whose action on the gastric secretion has not, to our knowledge, been studied previously, namely amidopyrine, aminopyrine or Pyramidon, as it is variously known. The reason for the inclusion of the latter in the present study was the experience of one of the authors with its spasmolytic properties (19, 20) and to a gradually growing conviction, based only on clinical observation, that its action is probably anticholinergic.

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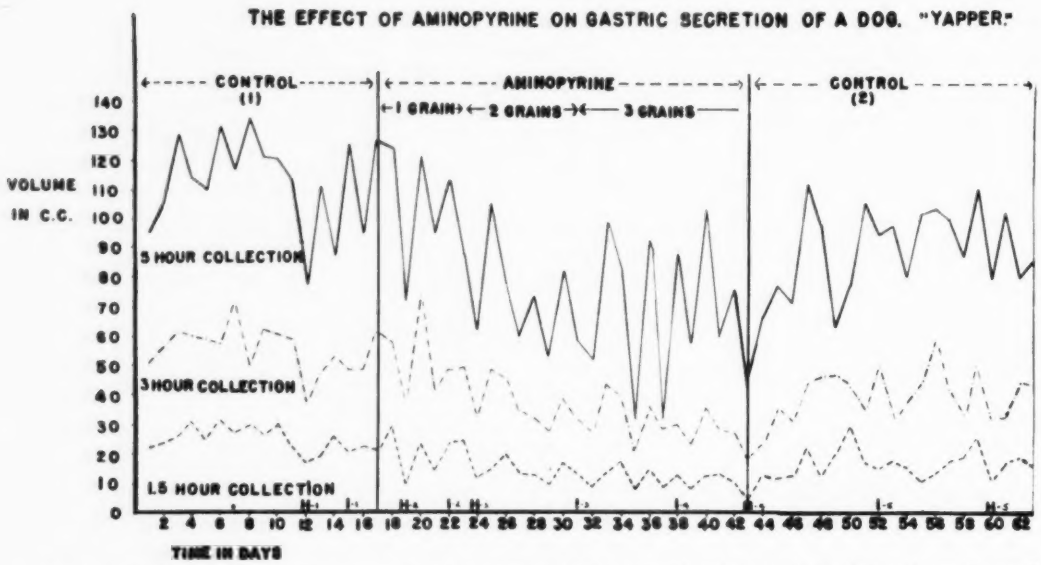

Fig. 1: Dog. No. 2. Note large volume of gastric secretion during control period; the daily fluctuations; the gradually increasing reduction in volume of secretion with increasing doses of amidopyrine; return of secretion to normal level after withdrawal of drug.

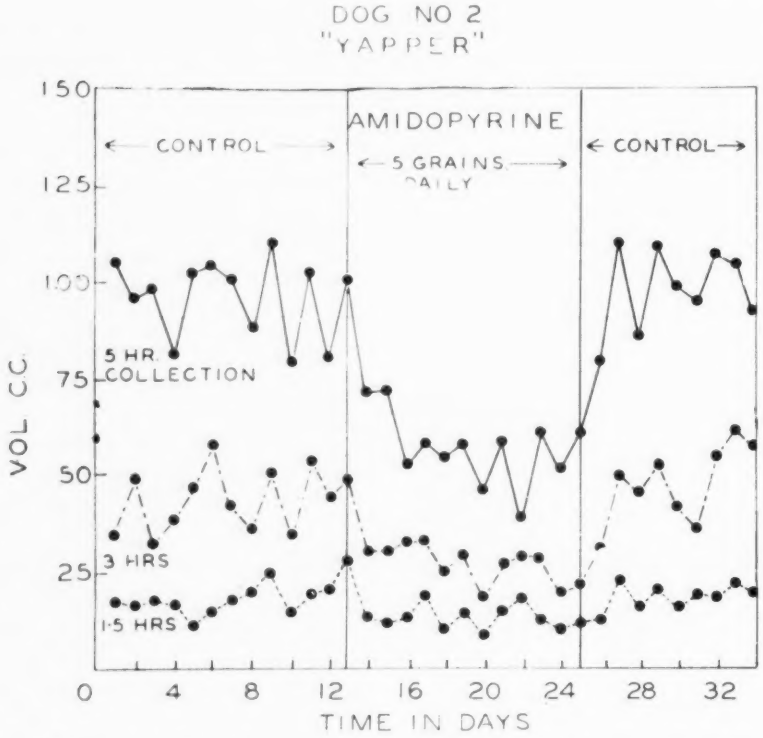

Fig. 2: Dog No. 2. Demonstrates the marked reduction in volume of gastric secretion following the administration of 325 mg of amidopyrine daily; and the rapid return of the secretion to normal after withdrawal of the drug.

METHODS

Three mongrel dogs with the vagally innervated pouches prepared by the method of Forse and Currie (21) were employed in these experiments. These pouches are fashioned from flaps obtained from the lower two-thirds of the anterior wall of the stomach. Throughout the course of this investigation the dogs were fed a synthetic diet supplemented with a daily allotment of 1.5 gm. of desiccated liver (21). The optimum quantity of this diet, once established, remained constant. This standardization was also carried through in the daily routine of the animals, and

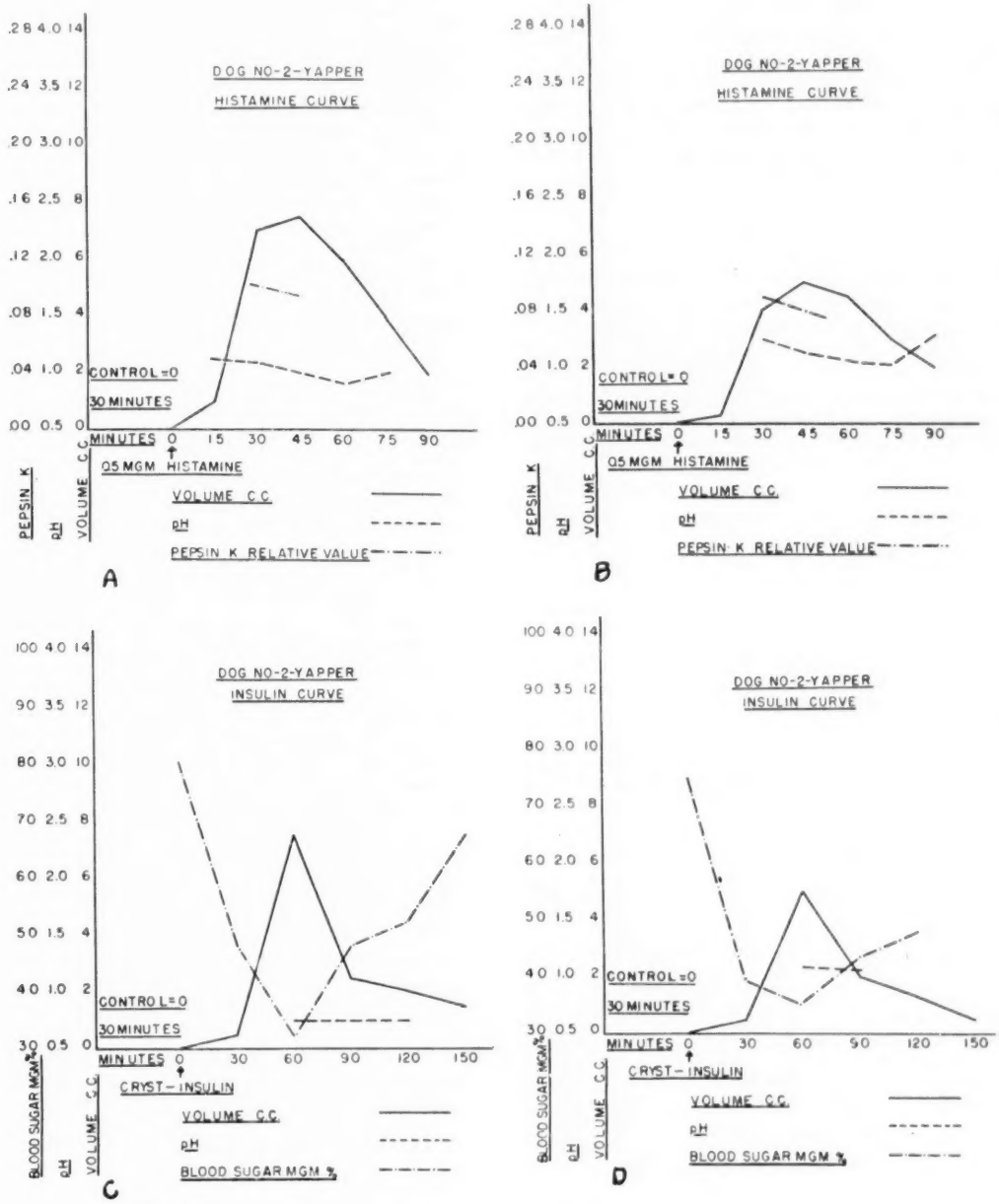

Fig. 3: Dog No. 2.
A. Control histamine test: large total volume; low pH; high pepsin.
B. Histamine curve one hour after 65 mg. amidopyrine; moderate reduction in volume.
C. Control insulin curve: marked fall in blood sugar; large volume secretion with low pH.
D. Insulin curve one hour after 65 mg. amidopyrine; reduction in volume secreted; slight elevation of the pH.

every effort was made to retain a constancy of significant factors.

The gastric pouch secretions were continuously collected during the test period into a flask attached over the stoma of the pouch, and connected to it by means of and indwelling cathether. The secretions were measured and determinations were made at the end of 1½, 3 and 5 hours after completion of the meal; the 1½ hour specimens and the secretions obtained in response to insulin hypoglycemia being considered to represent roughly the nervous phase, while the secretions obtained during the last 3½ hours and those obtained in response to histamine stimulation as similarly representing the chemical phase of gastric secretion. The volume and pH of the individual samples were determined, and the peptic activity established by the photoelectric method described by Riggs and Stadie (22).

RESULTS

The effect of amidopyrine on gastric secretion was studied in the three dogs. The results varied considerably, but were essentially similar in all three animals. The most pronouced effect occurred in dog No. 2 (Figs. 1 and 2). After a control period, a daily dose of 65 mg. of amidopyrine was administered orally, one hour before feeding. There was a slight reduction in the volume of gastric secretion and a similar effect was obtained following histamine and insulin stimulation (Figs. 2 and 3). There was no significant elevation of the pH in the daily gastric secretion; a slight elevation in the pH of the histamine and insulin secretions was noted. Increasing the dose of amidopyrine to 130 and to 195 mg. daily, resulted in further reductions in the volume of the gastric secretion (Fig. 1). Withdrawal of the drug was followed by a return of the secretion to normal or almost normal levels. After an adequate control period, the dose of amidopyrine was increased to 325 mg.; a still more pronounced reduction in the volume of gastric secretion resulted (Fig. 2). There was no significant difference in the effect on the nervous and on the chemical phase of the gastric secretion.

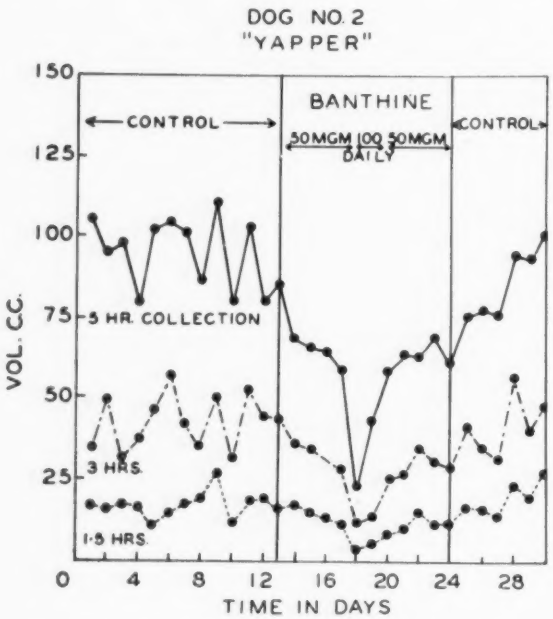

Fig. 4: Dog No. 2. Note reduction in the volume of gastric secretion effected by 50 mg. Banthine daily (orally), and the much greater reduction produced by doubling the dose.

The effect of oral administration of Banthine was studied in a similar manner in all three dogs. The results varied slightly quantitatively but were similar in the general pattern of response in all three animals. The findings obtained in dog No. 2 are presented to facilitate comparison with the results obtained with amidopyrine in the same animal. A daily oral dose of 50 mg. of Banthine was instituted after a control period; it was administered one hour before feeding. There was a significant reduction in the volume secreted—a drop from an average level of 95 cc. to 65 cc. Doubling the dose of Banthine resulted in lowering of the volume to a still greater degree (Fig. 4). Withdrawal of the drug led to a rapid return to the control level. The pH of the daily secretions rose slightly, especially in the nervous phase—from 1.0 to 1.3 (Fig. 5).

The effect of Bellafoline was studied in two of the dogs, the drug being administered intramuscularly. A daily dose of 0.1 mg. was injected 15 minutes before feeding. This produced a precipitous drop in gastric secretion from an average of 110 cc. to 40 cc. daily, the reduction occurring during the nervous phase being more pronounced than during the chemical phase. Return of the secretion to the normal level occurred on withdrawal of the drug (Fig. 6). There was a marked reduction in the histamine response (Figs. 7a and b), and a similar reduction in the insulin hypoglycemia response. There was no significant change in the pH in either case. The results obtained were similar in both dogs—the findings in dog No. 4 are given. These results are similar to those obtained with subcutaneous administration of Banthine, although somewhat less pronounced (23). Table No. 1 shows typical responses in dog No. 2 to insulin and histamine tests in control studies and following amidopyrine and Banthine respectively. Table No. 2 represents a 4½ month continuous study period in dog No. 4. It demonstrates the typical insulin and histamine response to varying amounts of amidopyrine and to 50 mg. Banthine respectively in dog No. 2 and to amidopyrine and Bellafoline in dog No. 4.

It was observed that the effect of Bellafoline began to wear off toward the end of the 5 hour period. Half-hourly collections indicated that this actually occurred about 3 hours after injection, the secretory rate returning to normal level within 3½ hours. The subcutaneous administration of Banthine results in a secretory depression lasting up to 5½ hours (23).

The description of the effect of amidopyrine on the gastric secretion is not to be construed as recommendation of the drug for this purpose. It is merely desired to record this finding, since the possibility of such action was raised in a study dealing with the spasmolytic properties of this drug (24). The authors also wish to stress the potential capacity of amidopyrine to cause granulocytopenia of varying degrees in susceptible individuals.

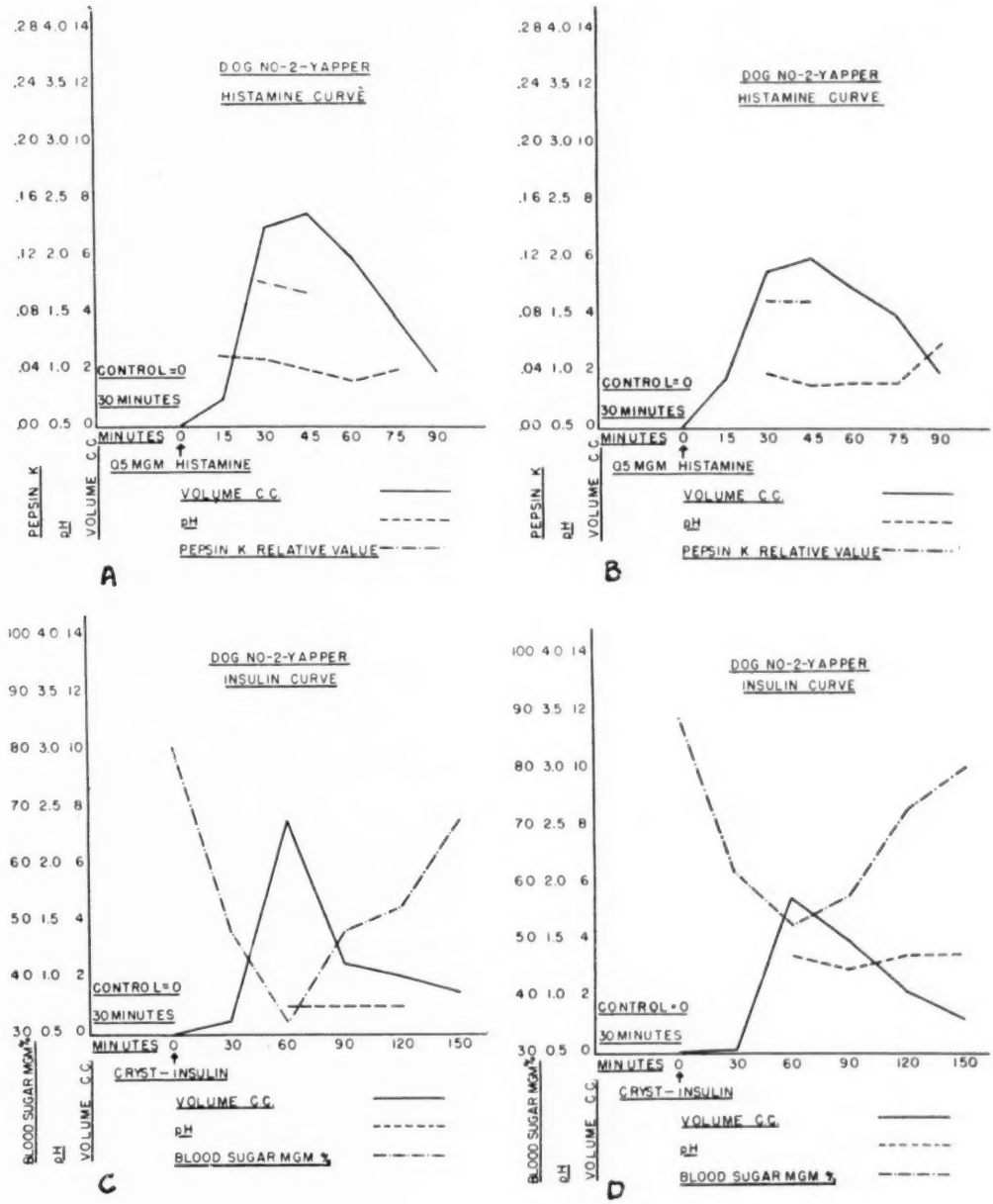

Fig. 5: Dog No. 2.
A. Control histamine curve: large volume; low pH; high pepsin.
B. Histamine curve one hour after 50 mg. Banthine; slight reduction in volume secreted.
C. Control insulin curve: large volume of low pH.
D. Insulin curve one hour after 50 mg. Banthine: reduction in volume of secretion; elevated pH.

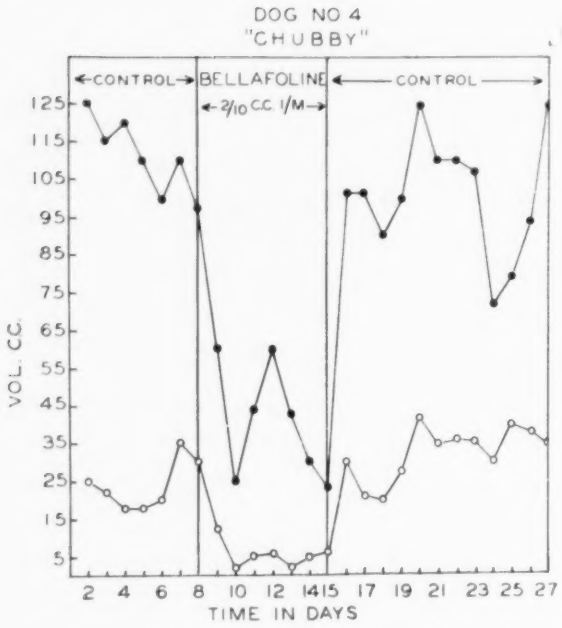

Fig. 6: Dog No. 4. Note marked reduction in the volume of gastric secretion following the administration of 0.1 mg. Bellafoline intramuscularly. The circles indicate the 1½ hr secretion, the dots the 5 hr. secretion.

CONCLUSIONS

1. Amidopyrine administered orally to dogs with innervated gastric pouches, produces a reduction in the volume of gastric secretion. The volume reduction increases with the larger doses employed, a 50% reduction with a dose of 325 mg. daily (the largest dose given). The reduction occurs in both the nervous and chemical phases.

2. The effect of Banthine is similarly dependent upon the strength of the dose, 100 mg. producing in the same animals over 50% reduction in the volume of gastric juice secreted.

3. Bellafoline in doses of 0.1 mg. administered intramuscularly, caused, in the same animal, a reduction of over 60% in the volume secreted by the pouch.

4. The degree of reduction in the volume of secretion produced by 100 mg. of Banthine, administered orally, required 325 mg. of amidopyrine similarly administered. Approximately the same degree of volume reduction is obtained with 0.1 mg. Bellafoline given intramuscularly.

5. The effect of amidopyrine and Bellafoline on the pH and pepsin values appears to be negligible; Banthine, on the other hand, causes a definite rise in the pH.

Aid in the pursuit of this study by Sandoz Pharmaceuticals Ltd., the Neo Drug Co. and by G. D. Searle and Co. is gratefully acknowledged.

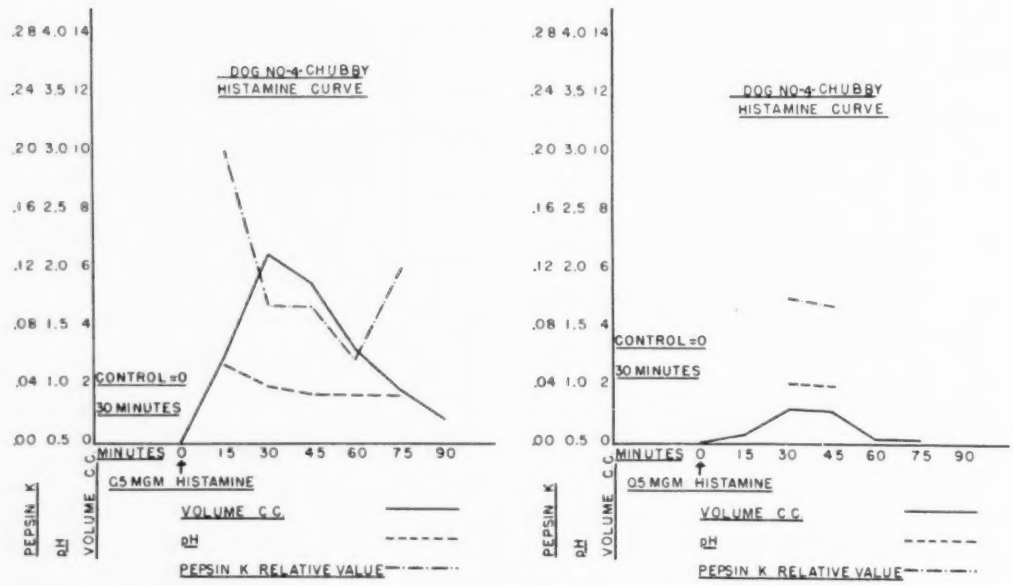

Fig. 7: Dog No. 4.
A. Control histamine test. Note large total volume; low pH and high pepsin values of the gastric secretion.
B. Histamine curve 15 mins. after 0.1 mg. Bellafoline intramuscularly. Note the marked reduction in volume of gastric secretion and the absence of significant change in the pH and pepsin values.

TABLE NO. 1

INSULIN TESTS

	Contr. p 0-30	Time in minutes 0-30	60	90	120	150
Control						
Vol. cc.	0	1	7.5	2.5	1.8	1.5
pH	0		0.75	0.75	0.75	
Blood sugar mg. %	80	48	32.5	47.5	51	67.5
After 65 mg. oral amidopyrine						
Vol. cc.	0	0.4	5	1.7	1	0.5
pH	0		1.1	1		
Blood sugar mg. %	75.5	38	34.5	44	46	
After 50 mg. oral Banthine						
Vol. cc.	0	0.05	5.65	3.9	2.1	1.3
pH	0		1.3	1.2	1.3	1.3
Blood sugar mg. %	87.5	62	52.5	56	73	79

HISTAMINE TESTS

	Contr. p. 0-30	Time in minutes 0-15	30	45	60	75	90
Control							
Vol. cc.	0	.9	7	7.7	5.5	4	2
pH	0	1.12	0.8	0.7	0.8	0.8	0
Pepsin	0	0.12	0.1	0.09			
After 65 mg. oral amidopyrine							
Vol. cc.	0	.04	4	5	4.5	3	2
pH	0		1.23	1.12	1.09	1.04	1.33
Pepsin	0		.09	.07			
After 50 mg. Banthine							
Vol. cc.	0	1.5	5.3	5.5	4.6	3.9	1.9
pH	0		.9	.8	.85	.81	1.25
Pepsin	0		.09	.09			

TABLE II

DAILY GASTRIC SECRETION AND THE GASTRIC SECRETION DURING HISTAMINE AND INSULIN TESTS

	Dys.	Dog No. 2		Dys.	Dog No. 4
Control period	12	100cc.*		11	80.6 *
		14 **			
		27 ***			
Amidopyrine gr. 3,lh.a.c.	3	66	6 gr.	8	57.3
		11.25			8.35 **
		19.2			25.9 ***
Second control period	12	95.4		5	79.9
		15.5			9.05
		35.4			16.25
Banthine 50mg. orally	11	63.7			
		12.6			
		23.7			
Control period	4	96		7	107.0
		13			
		20.9			18.3
Amidopyrine gr. 5	11	55.1	Bellafoline 2/10cc i.m.		43.0
		26.5			2.9
Control period	10	73.1			101.3
Amidopyrine - divided doses		58			
1½h. a.c. & 1½ & 3h. p.c.	8	8.4			
		25.9			

* Average volume in cc. of the daily gastric secretion.
** Total volume in cc. of the gastric secretion during insulin test.
***Total volume in cc. of the gastric secretion during histamine test.

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PRIMARY ADENOCARCINOMA OF THE APPENDIX*

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THE LITERATURE contains few references to the occurrence of primary adenocarcinoma of the appendix. The rarity of this lesion is an obvious fact. Since it is routine in all hospitals to examine removed appendices histologically, it would be easily recognized if adenocarcinoma did not occur so infrequently. Most texts on Pathology dismiss the subject with a sentence or two. In a careful study of the literature Lawton and Ehrlich (1) found only 22 cases of primary adenocarcinoma of the appendix and added 3 of their own. At the Mayo Clinic, Uihlein and McDonald (2) reviewed the records over a 30 year period and were able to find only five adenocarcinomas of the appendix. Sillery (3) quoting from seven sources found 116 cases of primary carcinoma of the appendix after eliminating those cases which might possibly be carcinoid. Lesnick and Miller (4) found the ratio of adenocarcinoma of the appendix to mucocele of the appendix and to carcinoid of the appendix to be 1:2:10 respectively.

At the Southern Division of the Albert Einstein Medical Center (formerly the Mount Sinai Hospital), we have encountered only one proven case of primary adenocarcinoma of the appendix in a 25 year period. Two other cases originally thought to be primary carcinomas of the appendix, on later detailed study were found to arise in the cecum and involve the appendix secondarily.

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Submitted February 6, 1953.

CASE REPORT

S. L., a 42 year old white man, machine operator, was first admitted to the Albert Einstein Medical Center, Southern Division, on May 11, 1951, complaining of pain in the right lower quadrant radiating over his entire abdomen. He had lost 14 pounds. He had enjoyed good health until 3 weeks prior to admission when he developed constipation. This was relieved only by enema; soon thereafter he noted a sharp stabbing pain in the right lower abdomen which radiated transversely and could be relieved by bowel movement. The pain recurred intermittently and at times became severe enough to cause him to "double up." There was no previous history of gastrointestinal disease, melena, or hematemesis. The past medical history was essentially negative. Physical examination revealed a normal blood pressure, temperature, pulse, and respiration. He was a comfortable, sthenic white male in no visible distress. Positive findings were limited to the abdomen and consisted of muscle tension in the right lower quadrant and the sensation of a circumscribed palpable mass. Laboratory studies were non-revealing. The impression of the admitting physician was (1) appendiceal abscess (2) possible carcinoma of the right lower colon (cecum) (3) carcinoid of the appendix (4) regional ileitis or (5) lymphoma. Barium enema showed a defect in the cecum due to extrinsic pressure. There was no evidence of regional ileitis. The patient was prepared with antibiotics for laparotomy and probable colon resection. At operation, the appendiceal area disclosed an indurated mass of what appeared to be carcinomatous tissue with several large nodes in the mesentery of the right colon. Several discrete nodules were present in the liver. A resection of the terminal ileum, right colon to midtransverse colon, including the lymph nodes in the mesentery, followed by an end to end anastomosis of the ileum to the mid-transverse colon was performed. The patient had an uneventful postoperative course and was discharged two weeks later feeling well and free from symptoms.

Pathological description:

Macroscopic: The specimen consists of 15 cms. of terminal ileum, attached to 30 cms. of colon. At the region of the base of the appendix, there is an invagination of the cecal pouch by a hard tan and yellow mass, measuring 4.0 x 3.0 x 2.0 cms. This produces, on the mucosal aspect of the cecum, an elliptical crateriform area, measuring 3.0 x 2.0 cms. in diameter, 1.5 cms. in depth, and with edges raised 0.6 cms. above the surrounding cecal mucosa. The surfaces of this area are smooth and glistening and appear to represent attenuated, but otherwise intact cecal mucosa. The crater leads into the orifice of the appendiceal lumen, which is widened for a distance of several millimeters. The proximal portions of the appendix are virtually completely obliterated by the mass described. The distal portions of the appendix are surrounded by extensions of the mass into the mesocolon. There is also extension into the wall of the distal 6.0 cms. of ileum, with replacement of the architectural markings of the outer portions of the wall. A number of globular lymph nodes, the largest measuring 2.0 cms. in diameter are present in the attached mesentery.

Microscopic: The mucosa of the appendix is the seat of a primary mucinous adenocarcinomatous process of moderately high grade malignancy (Figures 1 and 2). There are areas of extension far beyond the confines of the appendiceal wall, to involve the serosa of the adjacent terminal ileum and extend deeply in the cecum, as far as the mucosa. However, the cecal crater (Figure 3) is covered by intact cecal mucosa overlying the neoplastic elements, indicating extra-cecal origin. Tumor cells are seen in regional lymph nodes.

Pathological diagnosis:

Appendix: Primary extensive adenocarcinoma, with lymph node involvement.

Ascending Colon: Carcinomatous invasion of cecum.

Terminal Ileum: Serosal carcinomatous invasion.

Following his discharge from the hospital he gained 40 pounds, returned to work and felt well until November, 1951, five months following operation. At this time he redeveloped pain in the abdomen associated with nausea and vomiting. A

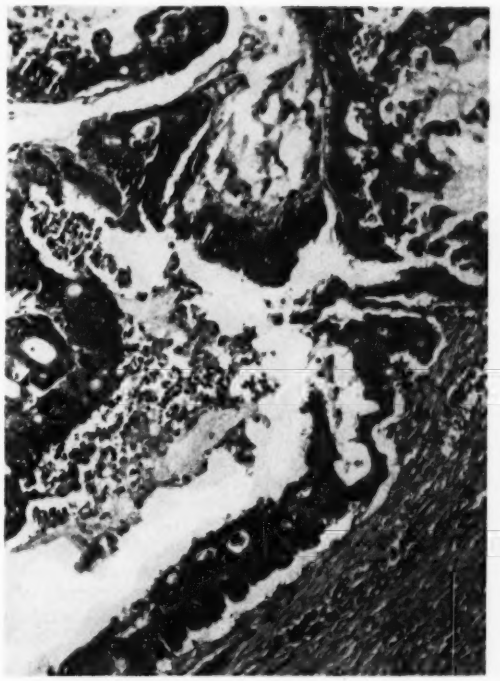

Fig. 2: Higher magnification of appendiceal mucosa showing carcinomatous transformation.

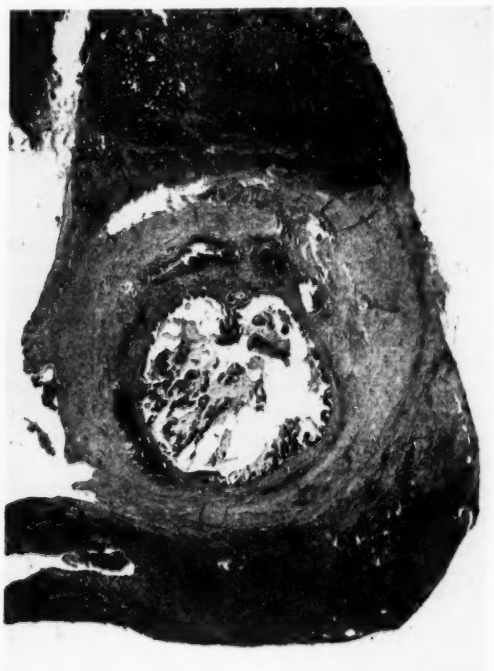

Fig. 1: Low power view of appendix and adjacent tissues showing papillary formations of appendiceal mucosal carcinomatous cells and dense involvement of periappendiceal tissue.

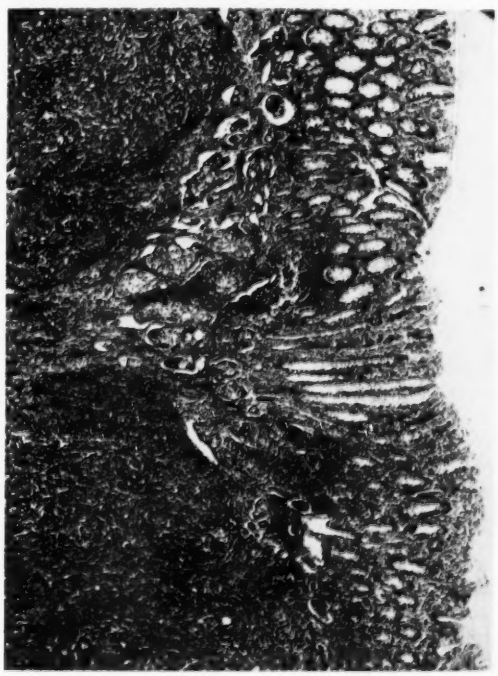

Fig. 3: High power view of bed of cecal "ulcer" showing intact colon mucosa and invasion of wall by carcinoma.

hard enlarged liver was now palpable. The abdomen gradually became distended and he had difficulty moving his bowels. Weight loss, anorexia, vomiting, ascites, metastases to the lungs, marked anemia with cachexia, and partial intestinal obstruction ensued. He expired on February 26, 1952 from widespread metastases, approximately ten months after the first symptoms of his disease.

Autopsy findings: Post-mortem examination performed three hours after death revealed marked emaciation and extensive metastatic carcinoma with marked involvement of the peritoneal surfaces (ascites 3000 cc.) and liver (weight 3750 grams). There was extensive mesenteric and retroperitoneal lymph node involvement. "Miliary" carcinomatous involvement of the lungs was also noted. Death was attributed to cachexia secondary to carcinomatosis.

DISCUSSION

Primary adenocarcinoma of the appendix may be fungoid or polypoid and is usually situated at the base of the appendix. It may produce obstructive symptoms. Spread is similar to that of carcinoma of the colon and occurs by direct extension and by way of the lymphatics or blood stream.

The clinical diagnosis of appendiceal adenocarcinoma is difficult and usually impossible. In most instances the patient is considered to have appendicitis or one of the complications of appendicitis. Frequently carcinoma of the colon is the clinical diagnosis. Even at the time of surgery with the lesion in view, the usual diagnosis is carcinoma of the cecum. This was all true in our case. Correct localization of the primary site was made only after careful study by the pathologist.

CONCLUSION

Primary adenocarcinoma of the appendix is a rare disease which produces no characteristic clinical symptoms other than that of appendicitis or of its complications. It usually defies preoperative diagnosis. In our hospital which is representative of the average general hospital, we have encountered only one proven case of primary adenocarcinoma of the appendix in a twenty-five year period.

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ABSTRACTS ON NUTRITION

HILL, K. R., RHODES, K., STAFFORD, J. L. AND AUB, R.: *Serous hepatosis: a pathogenesis of hepatic fibrosis in Jamaican children.* Brit. Med. J., Jan. 17, 1953, 117-122.

A liver disease occurring in Jamaican children is described and because of its clinico-pathological aspects, it has been named "serous hepatosis." To date, the only etiological factor which has been ascertained is a low protein intake. However, toxic factors may play a part, as well. It occurs in children usually between the ages of 1 and 3 years who present large, firm livers and ascites. Ultimately the appearance may be one of classical hepatic cirrhosis. Histologically, initial exudation or edema passes on to the deposit of eosinophilic coagulum which is finally invaded by fibroblasts.

REEVES, R. L.: *The role of lipid metabolism in atherosclerosis.* Bull. Mason Clin., 6, 4, Dec. 1952, 119-125.

Reeves reviews the current attitudes toward the title subject and notes that the beneficial effects of low fat and low cholesterol diets in atherosclerosis are sufficiently inconstant to suggest that many persons have an inherited abnormality of their lipid metabolism. It appears that indications for such a drastic diet remain limited until more definite proof of its value is forthcoming from laboratory and clinical study. The reduction of obesity, however, seems to be of value. Lipotropic agents are of little value in reducing either serum cholesterol or abnormal lipoprotein levels. While the cause of atherosclerosis remains unknown, it has recently been demonstrated that heparin alters the serum lipoprotein distribution rather profoundly, and this phenomenon is being intensively studied throughout the country.

MORRISON, L. M.: *Diet and atherosclerosis.* Annals Int. Med., 36, 6, Dec. 1952, 1172-1180.

Morrison produces rather convincing evidence that reduction of dietary fat, following coronary occlusion, cuts the mortality 50 percent in the first 3 years following the initial infarction. Furthermore, during the war years when European countries were heavily rationed on fats, deaths from arteriosclerosis, including coronary disease, fell off markedly, while in the U. S. A. death rates from the same causes continued an uninterrupted increase which began in 1935. Morrison is convinced that treatment of atherosclerosis should include a low cholesterol-low fat diet and the use of lipotropic agents to increase the serum phospholipid levels.

DUNCAN, G. G.: *Diabetic coma—a therapeutic problem.* Ann. Int. Med., 37, 6, Dec. 1952, 1188-1196.

Possibly the most important point in this contribution is that which refers to the author's method of deciding how much insulin to give a diabetic in coma. If the plasma acetone gives a grade 4 reaction, he uses 100 units of regular insulin as his initial dose. If the plasma on being diluted 1 to 1 with saline still gives

a grade 4 reaction, he starts with 200 units. If on this second dilution the same reaction is obtained, he starts with 300 units, and he starts with 400 units if the third dilution still gives a grade 4 reaction for acetone. Apparently Duncan has had no trouble with cerebral damage resulting from reduction of brain sugar.

RICKETTS, H. T.: *Basic principles in the therapy of diabetes.* Ann. Int. Med., 37, 6, Dec. 1952, 1181-1187.

Symptoms are easily relieved by diet and insulin, but normal nutrition must be achieved, and adiposity avoided or corrected. The remaining power of the pancreas should be preserved by keeping the blood sugar levels as near normal as possible, particularly in young diabetics. As for preventing the various complications, it appears that "good control" is the chief agent. The author refers to the work of Root and his associates as demonstrating a connection between good control and retardation of the appearance of complications.

WELSH, L.: *Failure of massive doses of vitamin B_{12} in acute leukemia.* Brit. Med. J., Nov. 22, 1952, 1133.

26 patients with various forms of leukemia were given very large doses of vitamin B_{12} varying from 2 to 130 mg., but none lived more than 5 months after beginning treatment. No complete remissions occurred, but 6 patients had partial remissions and 10 others reported feeling better. The prognosis or clinical course of acute leukemia obviously is not altered by adding vitamin B_{12} to other treatment.

BASU, A. K. AND NIYOGI, S. K.: *Use of absolute alcohol in post-operative cases by intravenous route, a preliminary report.* Calcutta Med. J., 49, 8, Aug. 1952, 303-305.

Twenty post-operative patients received alcohol intravenously in strengths varying from 5% in saline to 15 percent. In 2 cases 10 c.c. of absolute alcohol was given undiluted over a period of 3 or 4 minutes. Pulmonary complications were reduced. Patients also experienced a sense of well being. Gastrointestinal trouble was unusual (3 cases). In only one case was a thrombophlebitis produced. The stronger the solution, the more slowly was the alcohol administered.

KNODT, C. B.: *Antibiotics in the growth of ruminant animals.* Antibiotics and chemotherapy, 3, 4, Apr. 1953, 442-448.

Aureomycin increases the rate of growth, and may increase feed efficiency of dairy calves when fed at proper levels. Potassium penicillin does not increase growth rate and may be harmful at the levels fed to dairy calves. Procaine penicillin has not affected growth rates at the levels studied. The results with terramycin have been variable in calves under 8 weeks of age but in general produce a growth response. While aureomycin, penicillin and terramycin have been fed to lambs, the results are confusing and not yet conclusive.

BERGERON, G. A., BOURBEAU, G. AND DUGAL, L. P.: *Ascorbic acid and experimental hypertension in hypophysectomized rats.* Revue Canadienne de Biologie, 11, 5, March 1953, 484-490.

Experimental hypertension, produced by unilateral nephrectomy and daily injections of DCA and the use of saline as drinking water, is prevented very significantly by ascorbic acid, although the prevention is incomplete and delayed. Since the results are similar in hypophysectomized rats, it appears that the inhibition of DCA hypertension by ascorbic acid is independent of the pituitary gland.

WALKER, A. R. P. AND ARVIDSSON, U. B.: *The vitamin C content of braised cabbage cooked under pressure and prepared on a very large scale.* South African J. Med. Sci., 17, 3 and 4, December 1952, 143-144.

In the compound kitchens of the Witwatersrand gold mines, open cooking is being replaced by pressure cooking. Cabbage is the main source of vitamin C for the Bantu workers, among whom, incidentally, scurvy is very seldom found. One popular form of this vegetable is minced or quartered cabbage, braised in fat and then pressure cooked. Experiments are described which indicate that there is a good retention of vitamin C in such cabbage, even when prepared on a very large scale. The amount of the vitamin afforded, apart from that contained in the rest of the diet, well exceeds the present recommended allowance.

STOKSTAD, E. L. R.: *Antibiotics in animal nutrition.* Antibiotics and chemotherapy, 3, 4, Apr. 1953, 434-441.

The various antibiotics in small amounts can increase the growth rate of animals. This effect is largely mediated through their effect on the intestinal bacteria. Antibiotics may decrease the vitamin requirements and in some cases increase the utilization of certain types of protein supplements. Penicillin appears to decrease the requirement for biotin and folic acid but has no effect on the requirement for riboflavine, pyridoxine or pantothenic acid. Aureomycin reduces greatly the mortality rate in highly B_{12} deficient chicks. Antibiotics exert a complex effect on the intestinal microflora—they eliminate bacteria which produce harmful substances; they eliminate bacteria which absorb dietary factors and thus prevent their utilization by the host; finally, they enhance the bacterial synthesis of essential growth factors.

EDITORIALS

PROCTALGIA FUGAX

Sudden, severe rectal pain, without local or organic cause, is a more common symptom than the medical literature might lead us to believe. Ewing (1) has recently stated that physicians are very susceptible to it, although why this should be so, is not known. I think any physician, who analyzes his cases carefully, will encounter several instances of it every year. One of the outstanding features of proctalgia fugax is its temporarily unbearable nature. Relief is usually obtained by taking a plain warm water enema. However, Ewing claims that the simplest and most effective treatment is to eat something, or even merely drink a glass of water. This sets up the gastro-colic reflex which, in some way, abolishes the rectal spasm. When the pain comes on in the night, as it often does, it presumably is related to some unpleasant dream. Fortunately, proctalgia fugax is essentially harmless. Some twenty-five years ago one encountered very severe rectal pain in luetic patients and labelled it "rectal crisis." These attacks in tabetic patients lasted much longer, and were therefore anything but "fugax." In my own practice I have seen fewer and fewer tabetics in recent years, and not one case of rectal crisis for twenty years.

1. Ewing, M. R.: Proctalgia fugax. B. M. J., May 16, 1953.

DIARRHEAL DISEASES AS A NEW SPECIALTY

William Z. Fradkin (1, 2) of Brooklyn, may be right in his proposal that diarrheal diseases should constitute a sub-specialty under gastroenterology. It is unnecessary here to remind the reader of the still high mortality attending infantile diarrhea. Furthermore, it is unnecessary to state that adults suffering from chronic diarrhea, especially, frequently present problems which are not solved by the diagnostic methods usually employed. There can be little doubt that there are enough cases of diarrhea of undetermined origin to justify the establishment of diarrhea clinics in many large hospitals, as Fradkin suggests. One of the difficulties would be to ascertain and provide the peculiar qualifications for a diarrhea specialist. It might even occur to the general run of physicians that these qualifications might be difficult to find in one man, inasmuch as not only bacteriology, but gastroenterology, allergy, nutrition and endocrinology would be prime requisites. In fact, the field of diarrhea now is almost claimed by certain schools of psychiatry. Fradkin's chief contribution is the fact that he has brought to our attention in a forceful way the fact that diarrhea is not at present being treated with uniform intelligence or with startling success. The danger of establishing a specialty on a *symptom* is that not too many men would be willing to take it up.

1. Fradkin, W. Z.: Diarrheal diseases—a new specialty. N. Y. State J. M., 50, 17, Sept. 1, 1950.

2. Fradkin, W. Z.: The dietary treatment of diarrheal diseases. Amer. Jour. of Dig. Dis., 20, 7, 208-210, July 1953.

BOOK REVIEW

FIBROCYSTIC DISEASE OF THE PANCREAS. Martin Bodian, M. D., in collaboration with A. P. Norman, M. D., M. R. C. P., and C. O. Carter, B. M., M. R. C. P. Grune and Stratton, New York, 1953, $9.50.

A profusely illustrated book of 250 pages, the present volume is highly readable and advances the thesis that fibrocystic disease of the pancreas, affecting as it does the respiratory tract, the pancreas and the liver, is a congenital disorder of mucus production due to a recessive gene. 116 cases are studied and complete clinical details presented. 68 of the cases were fatal and 47 were living at the end of 1950. A diet high in protein and somewhat reduced in fat is employed. The value of pancreatin is *sub judice*, but it seems that pancreatin reduces the frequency of the stools and helps to improve nutrition. Control of respiratory infection is essential to preserve appetite, and without appetite the afflicted individuals soon deteriorate. The author believes that aureomycin will perhaps usher in a new chapter in therapeutics of this disease which almost always prevents the victim from reaching adulthood. It would appear that the disease is due essentially to a derangement of the cellular enzyme systems controlling mucus production and that this problem will require very special and prolonged attention, before ultimate success in treating the disease is accomplished.

GENERAL ABSTRACTS OF CURRENT LITERATURE

ROY, H. K. AND DAS, A.: *Terramycin in enteric fevers.* Calcutta Med. Journ., 49, 10, Oct. 1952, 389-392.

Of 25 cases of typhoid fever studied with a view to the effects of terramycin therapy, 15 were bacteriologically or serologically proved positive. In this limited group, results were excellent in 3 cases and good in 6 cases. Terramycin was thus successful in 60 percent of the proved cases. Chloramphenicol alone would have improved on these results. Both terramycin and chloramphenicol fail to prevent hemorrhage, perforation and miscarriage. Of the various complications arising during treatment, the authors feel that hematuria, oliguria and urinary retention, transient hepatitis and dermatitis may be due to the terramycin, but they are not dogmatic on this point. There were no relapses in the "proved" series, and on this score terramycin seems to have stolen a march on chloramphenicol.

BAKER, J. W. AND ANDERSON, R. F.: *Pancreatitis: the question of etiology and the problem of treatment.* Bull. Mason Clin., 6, 4, Dec. 1952, 133-156.

So far as we know, pancreatitis is due to bile reflux or to plugging or blockage of the pancreatic duct. The authors do not operate in acute pancreatitis, but merely estimate the serum amylase. In recurring pancreatitis, concurrent biliary tract disease is corrected, when possible. Where a common channel exists, a sphincterotomy of Oddi is done, leaving a long arm T-tube beyond the cut sphincter for from 3 to 6 months. If this fails, then transpleural sympathectomy on one or on both sides as pain dictates. If this fails, then the pancreas and duodenum are removed.

BOBROWITZ, I. D., ELIAS, F. AND OCHS, J.: *Gastrointestinal changes in pneumoperitoneum.* Am. Rev. Tuberculosis, 66, 6, Dec. 1952, 750-757.

A group of 37 patients with pneumoperitoneum had gastrointestinal studies performed immediately before beginning of treatment and again after 6 weeks and 6 to 8 months of collapse therapy. The typical anatomical changes which occurred with pneumoperitoneum included elongation and narrowing of the cardiac portion of the stomach, widening or dilatation of the fundus, anterior displacement and a drop of the stomach. Most patients lose weight with pneumoperitoneum. Other gastro-intestinal symptoms usually were mild. There was little correlation between the symptoms which occurred with pneumoperitoneum and the degree of anatomic changes resulting from the method.

DAVIDSON, L. S. P., GIRDWOOD, R. H. AND SWAN, H. T.: *Effect of ACTH and cortisone therapy in blood disorders.* Brit. Med. J., Nov. 15, 1952, 1059-1063.

ACTH or cortisone was given to 14 cases of purpura, to 2 cases of idiopathic acquired hemolytic anemia, and to a small group of patients suffering from aplastic anemia, leukemia or myelosclerosis. Three cases of thrombocytopenic purpura of short duration were apparently cured by hormone therapy. Temporary good effects were produced in 3 cases of idiopathic thrombocytopenic purpura and 2 cases of idiopathic acquired hemolytic anemia. Such remissions may be of value in allowing splenectomy to be undertaken with greater safety. No beneficial results were obtained in the remaining 8 cases of purpura and in a small number of patients suffering from aplastic anemia, acute leukemia or myelosclerosis.

FERGUSON, A. D. AND SCOTT, R. B.: *Anorectal examination of newborn infants (negro) with reference to the incidence of congenital strictures and status of anal sphincter tonus.* Arch. Pediatrics, 69, 10, Oct. 1952, 410-413.

In 500 consecutive, presumably normal Negro newborns, not a single instance of anorectal stricture was found. Apparently congenital anomalies are less frequent in Negroes than in the white race. There was considerable variation in anal sphincter tone.

O'BRIEN, G. F.: *Jaundice.* Ill. Med. J., 102, 5, Nov. 1952, 304-312.

In a review-type of article, O'Brien divides all jaundice into 3 classes—extrahepatic or hemolytic; intrahepatic; and extrahepatic or obstructive. The commonest type is the intrahepatic hepatocellular jaundice, and may occur in hepatitis, leading to cirrhosis. The physiological and biochemical changes associated with hepatocellular jaundice are described in some detail.

ALEXANDER, F. K.: *Duodenal ulcer in children.* Illinois Med. J., 102, 5, Nov. 1952, 285-286.

In children under 14, the incidence of duodenal ulcer is said to be about 5 percent. Pain of a vague character is characteristic, and nausea and vomiting common. The possibility of ulcer should be kept in mind in all cases of dyspepsia in children. Diagnosis is by means of x-ray. Careful medical, or at times, surgical treatment is needed. It is possible that many adult duodenal ulcers actually began in childhood.

BROWN, C. H., KANE, C. F. AND HARRINGTON, V. A., JR.: *Changes in surgery for carcinoma of the stomach,* 1940 through 1951. Cleveland Clinic Quart., 20, 1, Jan. 1953, 276-285.

"Clinical judgment" means little, exploration means everything because masses which clinically or by x-ray appear inoperable may sometimes be easily removed. Neither esophageal involvement nor metastases should interfere with radical surgery. "Metastases" are sometimes purely inflammatory. The operability and resectability rates have increased and this will result in more five year cures. More total gastric resections and more complicated resections with removal of adjacent organs are being performed.

STRITTMATTER, W. C. AND WISE, R. E.: *The roentgenologic diagnosis of jejunal or marginal ulcer.* Cleveland Clinic Quart., 20, 1, Jan. 1953, 286-291.

Marginal ulcerations with subsequent perforation may reach the unusually large size of 4 or 5 cm. in diameter. Characteristic radiating folds of jejunal mucosa frequently occur about the area of ulceration. Retention films should be made at 4 hours, and every one made has demonstrated barium in the ulcer crater.

BATEMAN, J. C., BARBERIO, J. R., CROMER, J. K. AND KLOPP, C. T.: *Investigation of mechanism and type of jaundice produced by large doses of parenterally administered aureomycin.* Antibiotics and Chemotherapy, 3, 1, Jan. 1953, 1-15.

In a clinical experiment to determine if aureomycin exerted a favorable effect in carcinoma, it was incidentally found that comparatively large doses of aureomycin glycinate parenterally administered, produced an intrahepatic obstructive jaundice, quickly reversible upon discontinuance of the drug. In some cases renal embarrassment also occurred. The icterus index and serum non-protein nitrogen determinations form a useful guide in therapy. (The effects of aureomycin on neoplasm are being reported elsewhere).

TURNBULL, R. B. AND MCCORMACK, L. J.: *Re-operated congenital megacolon.* Cleveland Clin. Quart., 20, 2, April 1953, 339-345.

A case of congenital megacolon is reported in which re-operation was performed because of retention of the aganglionic upper rectal segment. While resection of the dilated, hypertrophied colonic segment alone may temporarily restore bowel function for a number of years, retention of the aganglionic segment may eventually result in obstruction and recurrent megacolon requiring further surgery. Swenson's operation totally removes those portions of the rectum and lower colon in which no myenteric ganglia can be found.

WATSON, W. L.: *Cancer of the esophagus.* Am. J. Roentgen., Rad. Ther. and Nuclear Med., 69, 2, Feb. 1953, 191-195.

In a review of the surgery of esophageal cancer over a period of 25 years, it is obvious that much progress has been made. The operative mortality has been brought within reason, more patients are seeking help at a resectable stage of the disease, and the range of resectability has been extended. Serious operations are possible now in older patients. Palliative resection and gastroesophageal anastomosis with re-establishment of normal alimentation is a boon to the patient with incurable cancer of the esophagus.

WIGH, R. AND SWENSON, P. C.: *Photofluorography for the detection of unsuspected gastric neoplasms.* Am. J. Roentgen., Rad. Ther. and Nuclear Med., 69, 2, Feb. 1953, 242-267.

The authors were the first in America to attempt to uncover unsuspected gastric cancer by the photofluorographic method, beginning their work in 1947. Their method is simple, accurate and popular, as well as inexpensive, and is shown to be capable of spotting unsuspected gastric carcinoma and some of its precursors.

PELNER, L. AND WALDMAN, S.: *"Replacement" therapy versus "occupation" therapy with adrenal steroids in liver disease.* Amer. Pract. & Dig. Treat., 3, 12, Dec. 1952, 976-981.

Three cases of acute hepatitis were markedly benefitted by small doses of cortisone as the major element in treatment. Only 12.5 mg. twice daily were used. It is believed that the customary large doses of cortisone would have produced unfavorable effects.

KAHN, A., JR.: *The relationship of trauma to peptic ulcer.* J. Arkansas Med. Soc., XLIX, 7, Dec. 1952, 114-115.

Perforation of peptic ulcers does occur as a result of external trauma to the abdomen, or as a result of lifting or straining. Yet mathematically and from the standpoint of physics this is impossible. The Arkansas Workmen's Compensation Commission has awarded compensation in only 4 of 12 such cases. (Since it is well known that even moderate trauma to the abdomen in a healthy person can produce perforation of a normal gut, it seems remarkable that the validity of ulcer perforation under similar trauma should so frequently be denied—Reviewer)

LLOYD-THOMAS, H. G. L. AND SHERLOCK, S.: *Testosterone therapy for the pruritus of obstructive jaundice.* Brit. Med. J., Dec. 13, 1952, 1289-1291.

Methyltestosterone, 25 mg. daily sublingually, relieved pruritus within 7 days in 7 patients suffering from chronic obstructive jaundice. The rationale of this therapy is not known. Other effects of prolonged testosterone therapy were an increase in the depth of the jaundice, a fall in the serum cholesterol level, and masculinization in 3 of the 6 female patients treated.

NUESSLE, R. F.: *Tumors of the small bowel.* Journal-Lancet, Jan. 1953, 12-15.

The most important single factor in the diagnosis of tumors of the small intestines is the ability of the physician to suspect their presence. Diagnosis of tumor of the small gut should be attempted whenever persistent gastro-intestinal symptoms cannot be otherwise explained. Occult bleeding occurs early and its detection is important. X-ray studies should always be made when abdominal pain, vomiting, melena or diarrhea are not explained by routine examination.

BETTS, J. W. AND ROWLANDS, B. C.: *Leaking abdominal aneurysms; two unusual cases.* Brit. Med. J., Jan. 10, 1953, 73-75.

Two cases of ruptured aortic aneurysms are described which presented clinically as incarcerated herniae. In each case the aneurysms had ruptured low in the abdomen, the blood had extravasated retroperitoneally and tracked down along the iliac vessels through the femoral canal and along the spermatic cord.

BRUWER, A. AND HODGSON, J. R.: *Intestinal obstruction in fibrocystic disease of the pancreas.* Am. J. Roentgen., Rad. Ther. & Nuclear Med., 69, 1, Jan. 1953, 14-21.

Intestinal obstruction complicating fibrocystic disease of the pancreas may be due to meconium ileus; to impaction of the meconium, with atresia or volvulus or both; or it may occur in infancy, well after the period when the term "meconium ileus" is applicable. It is suggested that a comprehensive term such as "infantile pancreatic ileus" would indicate intestinal obstruction associated with cystic fibrosis of the pancreas. Calcification in the abdomen of a newborn child is, for practical purposes, indicative of a previous fetal peritonitis, one of the causes of which is obstruction complicating fibrocystic disease. Operation for meconium ileus is no longer uniformly fatal.

SCOTT, W. G. AND SIMRIL, W. A.: *Neweer radiopaque media for oral cholecystography.* Am. J. Roentgen., Rad. Ther. and Nuclear Med., 69, 1, Jan. 1953, 78-87.

Telepaque seems in many ways to be superior to priodax or monophen in cholecystography. Telepaque may be ingested in the morning and satisfactory pictures obtained the same afternoon. It can be given immediately after the barium meal in the morning and good pictures can be made 4 to 6 hours later, although, for obvious reasons, this is not suggested as a routine procedure. What is most interesting is that the authors found they could have the patients take Telepaque with the usual evening meal, without subjecting them to a restricted diet or to a complicated ritual of behavior. Very satisfactory pictures resulted even when the tablets were taken with an evening meal rich in fats. Another advantage of Telepaque is the visualization of the cystic, hepatic and common ducts on pictures made 5 to 15 minutes after the fat meal.

BRICK, I. B.: *Practical investigation of diarrhea.* Am. Pract. & Dig. Treat., 4, 1, Jan. 1953, 35-38.

Among the valuable remarks contained in this short article are the following—in a patient with diarrhea of many years' duration and with little or no weight loss, the cause usually is the irritable colon syndrome; it is probably safe to say that if diarrhea occurs at night, the cause is organic; aureomycin, terramycin, digitalis, iron and other drugs may be responsible. Food allergy as a possible cause of diarrhea is not mentioned.

JONES, F. A. AND DOLL, R.: *Treatment and prognosis of acute perforated peptic ulcer.* Brit. Med. J., Jan. 17, 1953, 122-127

A series of 715 patients with perforated peptic ulcers, from 1938 to 1951 is reported. Three methods of treatment are considered—gastric aspiration, surgical closure and immediate partial gastrectomy. There is no evidence that any one method should be used routinely, as they all have merit. When aspiration is used it must be done expertly. The value of partial gastrectomy is that an unrecognized carcinoma of the stomach may be eliminated. Simple closure is valuable where the general condition of the patient prohibits the major procedure.

MILTON, G. W.: *The occurrence of secondary malignant disease in the spleen.* Med. J. Australia, Nov. 22, 1952, 736-740

In a series of 3620 autopsies, microscopic examination of the spleen was done in every case. Malignant disease was present in the bodies of 653 cases, and in 25 of these there were demonstrable secondary deposits in the spleen. Secondary deposits in the spleen in any case of malignant disease indicate a bad prognosis, since splenic deposits occur only in those cases in which widespread arterial-borne metastases have appeared. Malignant seedlings grow poorly in the spleen.

SHAW, F. H. AND PETERSON, G. T.: *Intra-abdominal use of penicillin.* Med. J. Australia, Nov. 22, 1952, 742-744.

The production of a suitable diluent for penicillin for topical use was found to be equal parts of lactose and calcium gluconate. Animal tests revealed a penicillin blood level of 0.4 unit per milliliter, seven hours after it had been placed in the abdominal cavity, and 0.05 unit at an interval of 24 hours.

GUHA, P., BHATTACHARYA, I. B. AND BHADRA, N. C.: *Treatment of chronic bacillary dysentery with sulfabenzide (sulphanilybenzamide).* Calcutta M. J., 50, 1, Jan. 1953, 16-22.

Eight cases of chronic bacillary dysentery are described in some detail, their duration being from one to several months. Sulfabenzide (Bengal Immunity Co., Ltd.) was found fully as efficacious in acute as in the chronic disease. Adjuncts used in treatment included iron, protein, hydrolysate, vitamins and liver extract. It was found that best results were obtained when treatment was begun early. The total amount of the drug was from 15 to 20 grams.

BARCLAY, S.: *Carcinoma of the large intestine.* New Zealand M. J., LI, 286, Dec. 1952, 394-400.

In reviewing the results of surgery in 37 cases of malignant neoplasm of the colon, Barclay finds today that the patient with such a lesion has about an even prospect of being cured, with less incidental risk and a shorter recovery period than formerly. He emphasizes the importance of physiological restitution prior to operation.

ROTH, H. P., FERRERI, R. N., PETTI, N. A. AND EVANS, M. W.: *Motility of the small intestines during emotional reactions.* Ann. Int. Med., 38, 1, Jan. 1953, 38-52.

The motility of the small intestine was recorded by the balloon-tambour method in 2 patients during psychiatric interviews in which emotional reactions were elicited. Significant emotional reactions were observed on 34 occasions. During only 7 of these was there simultaneously a definite change in intestinal motility. No characteristic pattern of intestinal motility was consistently associated with any specific emotion, although there seemed to be a tendency for anger to be associated with increased tone.

DIODRAST TERMED CHOICE AGENT IN STUDYING FETAL PHYSIOLOGY

Amniography with 70 per cent solution of Diodrast as the contrast medium provides more valuable information on fetal physiology, without systemic reaction, than any other known method of examination, according to Dr. Eugene M. Savignac, Detroit, Michigan. He writes in *Radiology* (60:545, April 1953).

In a comprehensive paper on roentgen amniography, Dr. Savignac reports on the effectiveness of this technique in providing important information concerning the status of pregnancy. Fetal soft-tissue abnormalities, fetal gastrointestinal activity, fetal life or death, malformations in the lumen or walls of the uterus and placental implantation can be determined by this technique. At the same time maternal excretory urography is made possible. The knowledge obtained of certain conditions cannot be diagnosed clinically or by other radiographic means, he states.

A significant finding in the study of 10 pregnant women at Holy Cross Hospital in Detroit, he adds, is that amniography with 70 per cent Diodrast was harmless to mother and fetus and "did not seem to induce labor."

He describes the technique as a method of obstetrical diagnosis involving transcutaneous puncture of the uterus through the maternal abdominal wall to inject varying quantities of Diodrast into the amniotic cavity. The amount of Diodrast injected depends upon the quantity of amniotic fluid. In general clinical practice amniography is done in the last three months of pregnancy, although it has been used earlier experimentally, he notes.

The radiologist is able to detect gross abnormalities of fetal soft tissues appearing as negative shadows in the opaque amniotic fluid. Fetal sex might thus be detected before birth, Dr. Savignac says. Every live fetus swallows the injected Diodrast, which appears in its digestive tract, and failure of swallowing "presumably indicates fetal death."

The contrast agent is eliminated by the maternal urinary tract, providing an excretory urogram about three hours following uterine puncture, the author continues. In addition, placental implantation is shown "very definitely" at any stage of pregnancy and with any position or presentation of the fetus.

WINTHROP ACQUIRES NEW BUILDING AS MID-WEST SALES, SHIPPING HQ.

A modern, new building located at 2020 Greenwood Street, Evanston, Ill., has been acquired by Winthrop-Stearns Inc., pharmaceutical manufacturer, to serve as its branch sales and shipping headquarters in the Mid-West, it was announced by Dr. Theodore G. Klumpp, president.

The structure was purchased in order to furnish the drug firm with larger facilities to expand its service to the medical profession and drug trade throughout the midwestern states. Operations in the new premises commenced in July, coincident with the closing of Winthrop's former headquarters at 445 Lake Shore Drive in Chicago.

A modern, one-story building, it has a 340-foot frontage and a depth of 150 feet, with total working space of 51,000 square feet. It will house Winthrop's commercial sales office, professional service office and warehouse. Robert A. Jarecki is branch manager.

The warehouse will stock Winthrop's complete line of ethical pharmaceutical products. Truck docks have been constructed within the building proper, to provide maximum convenience in loading and unloading operations under all weather conditions.

NOTICE

BIO-RAD LABORATORIES, Berkeley, California, establishes a new service offering ultracentrifugal analysis and separation to industrial organizations, research laboratories, and consulting groups. Combining the availability of qualified investigators with both analytical and preparative ultracentrifugal equipment, the new service is established to provide special advantages for petroleum and pharmaceutical research and analytical groups; educational, government, and high-polymer chemical-manufacturing organizations. Among the specific services available are analyses of molecular-weight distribution, homogeneity, and purity in centrifugal fields up to 260,000 times gravity and over the molecular weight range from 300 to high polymers—as well as preparative separation of molecular species, structural isomers, and particle sizes—in fields up to 140,000 times gravity.

PARKE, DAVIS & COMPANY REPORTS NET SALES OF $53,674,407, NET EARNINGS OF $4,312,981 FOR FIRST SIX MONTHS OF 1953

DETROIT, JULY 28—Parke, Davis & Company, world-wide pharmaceutical firm, today reported net sales of $53,674,407 and net earnings of $4,312,981 for the first six months of this year.

In its interim statement for the first six months of 1952, the 86-year-old company reported net sales of $70,739,771 and net earnings of $9,778,861. Harry J. Loynd, president, explained that decreased antibiotic sales were mainly responsible for the declines this year.

He said, "Sales of our products other than antibiotics are at a higher level than for the same period of 1952, and this trend should continue throughout the remainder of the year."

The net earnings for the first six months of this year equalled 88 cents on each of the 4,894,900 shares outstanding.

Parke-Davis, which has made a profit every year since 1876, had net sales of $28,195,757 in the first quarter and $25,478,650 in the second quarter of this year. Net earnings in the first quarter totalled $2,209,957 and in the second quarter, $2,103,024.

On July 31, the firm will make its 263rd consecutive dividend payment to more than 24,000 stockholders, none of whom has as much as four percent of the shares outstanding. The payment to stockholders of record July 3, 1953, will amount to 35 cents a share.

Loynd said in his letter to the stockholders, "Our levels of costs, expenses, inventory investments, and plant and equipment requirements will continue under critical review in the light of present trends and conditions. It will be appreciated, however, that readjustments in these categories must also recognize long-range objectives and re-

quirements of a company that intends to progress in the future as it has in the past, despite the present temporary setback from which I feel we will gradually recover."

NEW FOLDER CONTAINS PUBLIC SERVICE MESSAGES ON PROMPT AND PROPER MEDICAL CARE

DETROIT — Parke, Davis & Company, responding to requests for reprints, has published a folder containing the first four in its new series of public service advertisements on the importance of prompt and proper medical care.

More than 50,000 copies of the folder already have been distributed. The national messages caution against neglect and delay in seeking the physician's help. They cite symptoms of specific diseases and emphasize, "In the hands of your physician, you're in good hands."

Leaders in the medical profession and various state and county medical societies have endorsed the messages.

Ralph G. Sickels, director of advertising and public relations for the pharmaceutical firm, said, "We like to think these public service advertisements may be more truly helpful to people than almost any other ad they run across. The messages are the latest in a campaign we started 25 years ago this month —an effort to make the subject of prompt and proper medical care 'come alive' to the man on the street, the woman in the home.

"It is gratifying to have this advertising spoken of as performing a distinct public service. We like to get 'high readership' ratings from organizations equipped to measure and evaluate the extent to which advertising is seen and read.

"Most of all, though, we are pleased to get almost daily evidence that these advertisements seem to be nudging people into action—and that the specific examples we are citing about the tragic consequences of delay are helping to generate among people a heightened respect for the professions of medicine and pharmacy."

NOTICE

Dr. Robert S. Goodhart, Scientific Director of the National Vitamin Foundation, Inc., announced today that the Foundation is moving from its present location at 150 Broadway to more adequate quarters at 15 East 58th Street, New York 22, N. Y., and will be in operation at that address from August 1, 1953.

A. P. H. A.

News of latest developments aimed at preventing disease and promoting personal and public health will be exchanged by professional workers from all parts of the free world at the 81st annual meeting of the American Public Health Association and annual sessions of 40 related organizations at the Hotel Statler and New Yorker, New York City, November 9-13.

More than 5,000 public health workers—physicians, dentists, nurses, engineers, statisticians, veterinarians, sanitarians, nutritionists, health educators, entomologists, biologists and others—are expected to attend the sessions, according to the Association's executive secretary, Dr. Reginald M. Atwater. Theme of the meetings will be "Meeting the Health Needs of the Community."

"The Association's annual meetings serve to bring to the attention of professional workers in the field of public health the latest findings and views of their fellow workers and thus to stimulate further research and development," Dr. Atwater said in announcing the plans.

"Year after year, milestone after milestone in public health progress has been recorded at these meetings as man has won battle after battle in the ceaseless war against disease." Dr. Atwater added: "At the 1952 annual meeting in Cleveland, for instance, conclusive findings were first released on the use of gamma globulin to prevent poliomyelitis. Again this year, we look forward to hearing news that will bring new hope for longer, healthier, happier life to people everywhere."

Among areas in which progress reports are scheduled, according to Dr. Atwater, are further developments in use of gamma globulin for polio prevention, mass vaccination against influenza, fluoridation of food and water supplies, new methods of tuberculosis treatment and care, and integration of mental health in public health departments.

Sessions will be devoted to industrial hygiene and sanitation, school health programs, nutrition and dietary developments, control of animal disease, maternal and child health, accident prevention, home nursing, laboratory and engineering developments, and work with handicapped children of various types.

Highlights of the sessions will be presentation of the Sedgwick Memorial Medal for distinguished service in public health, scheduled for Wednesday evening, November 11, and presentation of the Lasker Awards for 1953 for outstanding contributions in medical research and public health administration, scheduled for Thursday afternoon, November 12.

Local arrangements for the Annual Meeting are being made by a committee headed by by Dr. John F. Mahoney, commissioner of health of New York City, and Dr. Herman E. Hilleboe, commissioner of health of New York State.

4,000 PARKE-DAVIS EMPLOYES WILL BE GIVEN UNIQUE PLANT TOURS OF DETROIT FACILITIES

DETROIT—Approximately 4,000 employes of Parke, Davis & Company will see how their individual jobs fit into the drug firm's overall operations during unique plant tours here in the next six weeks.

The employes, who will be paid for the time required to make the tours, will take the trips during regular working hours.

"This new approach to plant tours will show employes how their particular operations contribute to our final products," according to Harold K. Daniels, personnel relations director.

"In addition," Daniels said, "the tours are part of an expanded program enabling employes to learn more about the company's history, production and research laboratories and products."

He explained that eight groups of 15 each would be taken on the daily tours, which will last four hours and include a refreshment break in the company's snack bar.

Daniels said daily production would be maintained, because only a limited number from each department would be assigned to the groups at a time.

Special plant guides, who conduct regular company tours for medical and pharmaceutical groups,

"It's a great relief . . ."

and 8000 doctors agree*

For acid indigestion, heartburn, bloating, belching and dyspepsia, 8000 doctors say they rely on Creamalin, *the reactive gel*, to give relief.

Because it is reactive,
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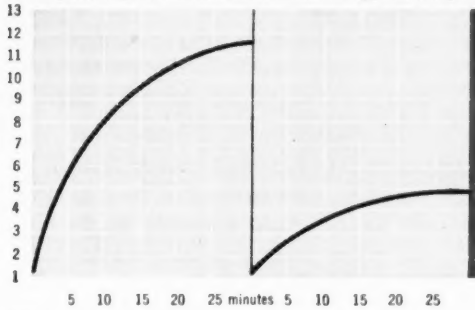

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Creamalin—in pregnancy heartburn
Creamalin tablets act without acid rebound or electrolyte imbalance, cause no fluid retention. They add virtually no calories. Palatable and of smooth consistency, Creamalin tablets are easy to take. Prescribe as often as necessary.

1. *Woldman, E. E.:* Am. Jour. Med. Sc., *194:333, Sept., 1937.*
2. *Smith, F. H.:* Gastroenterology, *8:494, Apr., 1947.*

Winthrop-Stearns INC. New York 18, N. Y. Windsor, Ont.

*Answers to a questionnaire recently mailed to 65,000 physicians
Creamalin, trademark reg. U. S. & Canada, brand of aluminum hydroxide gel

Meat...

and the Diet after 50

Although caloric needs in the later decades of life lessen with decreasing physical activity and diminishing metabolic rate, clinical observations[1] corroborated by experimental studies[2] show that protein needs of the aging organism continue at the levels of adequacy in earlier years.[3] For avoidance of protein deficiencies, which the aged are prone to develop,[4] the protein quota of the diet of persons over fifty should be more liberal than is often the practice.[5] In providing this quota, lean meat may well be one of the protein foods of the daily diet.

In the years beyond fifty, as well as before, continuous adequate protein nutrition remains an absolute necessity for maintenance of a normal concentration of plasma proteins and, in turn, a normal osmotic pressure of the plasma.[6] Even more pronounced in the aged than in younger persons are the ill consequences of hypoproteinemia—edema, decreased resistance to generalized infection, retarded bone healing, and poor wound healing.[7] Furthermore, dietary protein is essential for the continuous chemical regeneration of cell protein in the prevention of abnormal tissue wasting, one of the most characteristic and obvious changes in the geriatric patient.[8]

But meat is much more than an outstanding protective protein food in the dietary of persons over fifty. It also supplies generous amounts of the B group of vitamins and of iron, phosphorus, and other essential minerals. In the well-balanced diet of the later years of life, meat is just as important for the maintenance of nutritional and physiologic well-being as it is during the earlier years of life.

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The Seal of Acceptance denotes that the nutritional statements made in this advertisement are acceptable to the Council on Foods and Nutrition of the American Medical Association.

will explain the various manufacturing, research and administrative processes.

The tours will begin August 10, Daniels said, and, at the rate of 120 persons per day, will take approximately six weeks to complete.

More than 10,000 members of the medical, pharmaceutical and allied professions annually tour the large Parke-Davis laboratories in Detroit.

STUDY TERMS LEVOPHED VALUABLE IN TREATING VARIOUS FORMS OF SHOCK

Slow intravenous infusions of the vasopressor drug Levophed (levarterenol) were successful in elevating blood pressure out of severe shock levels in 30 of 32 patients, substantiating previous studies which attest to the importance of this agent in treating shock from various causes, according to an article in the Journal of the American Medical Association (152:1198, July 25, 1953).

All of the cases studied were gravely ill and in a state of shock associated with such conditions as acute myocardial infarction, acute coronary insufficiency, anaphylactic shock, pulmonary embolization, massive gastrointestinal hemorrhage, barbiturate intoxication, bulbar poliomyelitis, ruptured ectopic pregnancy, and others.

The ultimate prognosis in five patients was known to be hopeless, and Levophed was administered in many other instances only as a last desperate measure, report Drs. A. J. Miller, A. Shifrin, B. M. Kaplan, H. Gold, A. Billings and L. N. Katz. The study was conducted at Michael Reese Hospital, Chicago.

The investigators used Levophed in treating 40 episodes of shock in the 32 patients, nine of whom were in shock following acute myocardial infarction. "Excellent" pressor responses, classified as rising to normal limits, were obtained in 25 patients, while "moderate" blood pressure rises were effected in five. No responses were obtained in the remaining two cases.

"The results of the present study definitely establish Levophed as a valuable adjuvant in the treatment of shock," the doctors state.

They note that severe cardiogenic shock, with a mortality rate of more than 75 per cent, occurs fairly often after acute myocardial infarction. Intra-arterial transfusion combined with a vasopressor drug "may be a more effective therapeutic approach than any heretofore utilized," according to the report. It asserts that "in cases where intravenous administration of whole blood alone is not effective in reversing shock due to blood loss, the use of vasopressor therapy would appear to be mandatory.

"Further experience may establish that the immediate utilization of Levophed along with whole blood is the most conservative method of treating severe shock, the aim of good therapy being to reverse the state of shock as quickly as possible."

In addition, the study found that Levophed "may prove of increasing value in patients with persistent blood loss who require emergency surgery." Levophed, a pressor amine, was synthesized at the Sterling-Winthrop Research Institute and is supplied by Winthrop-Stearns, Inc.

The solution used in the study generally contained 4 micrograms of

Levophed per cc. prepared by adding four cc. of five per cent glucose in water. Greater concentrations of the vasopressor were prepared when it was desired to limit the total intake of fluid. No undesirable effects were noted, however, with doses as high as 100 drops per minute of a solution containing 32 micrograms of Levophed per cc.

Summarizing results of the study, the team states that Levophed did not increase myocardial irritability, and in no instance did it "precipitate or aggravate heart failure." They add that there were no apparent ill effects in patients digitalized before or during use of the drug.

Most dramatic result was achieved in a patient with anaphylactic shock, the blood pressure "being quickly raised from 40/0 to 110/80," following only one-half hour's treatment.

In eight of nine patients in shock accompanying acute myocardial infarction, excellent pressor responses were obtained, as in two or three cases of shock with acute myocarditis and another disease. Sixteen patients were treated for shock of non-cardiac origin.

FURACIN VAGINAL SUPPOSITORIES BRING NEW COMFORT TO WOMEN UNDERGOING RADIATION THERAPY

Furacin vaginal suppositories have proven effective in decreasing the vaginal discharge of 26 women undergoing X-ray or radium therapy to the pelvis for some type of malignant pelvic neoplasm like carcinoma of the cervix or vagina.

These results were reported by Dr. Jerome Schwartz, Lynbrook, N. Y. and Dr. Vincent Nardiello, Hicksville, N. Y. in the "American Journal of Obstetrics and Gynecology," May, 1953.

The doctors noted that vaginal discharge is usually a constant, persistent, and uncomfortable accompaniment of X-ray or radium therapy. "By reducing the vaginal infection, the Furacin vaginal suppositories contributed to a better response of the malignant tissue to a given unit of radiation," they stated. In only two cases was sensitivity observed, and in one of these it occurred only after nine months of almost constant use of Furacin vaginal suppositories.

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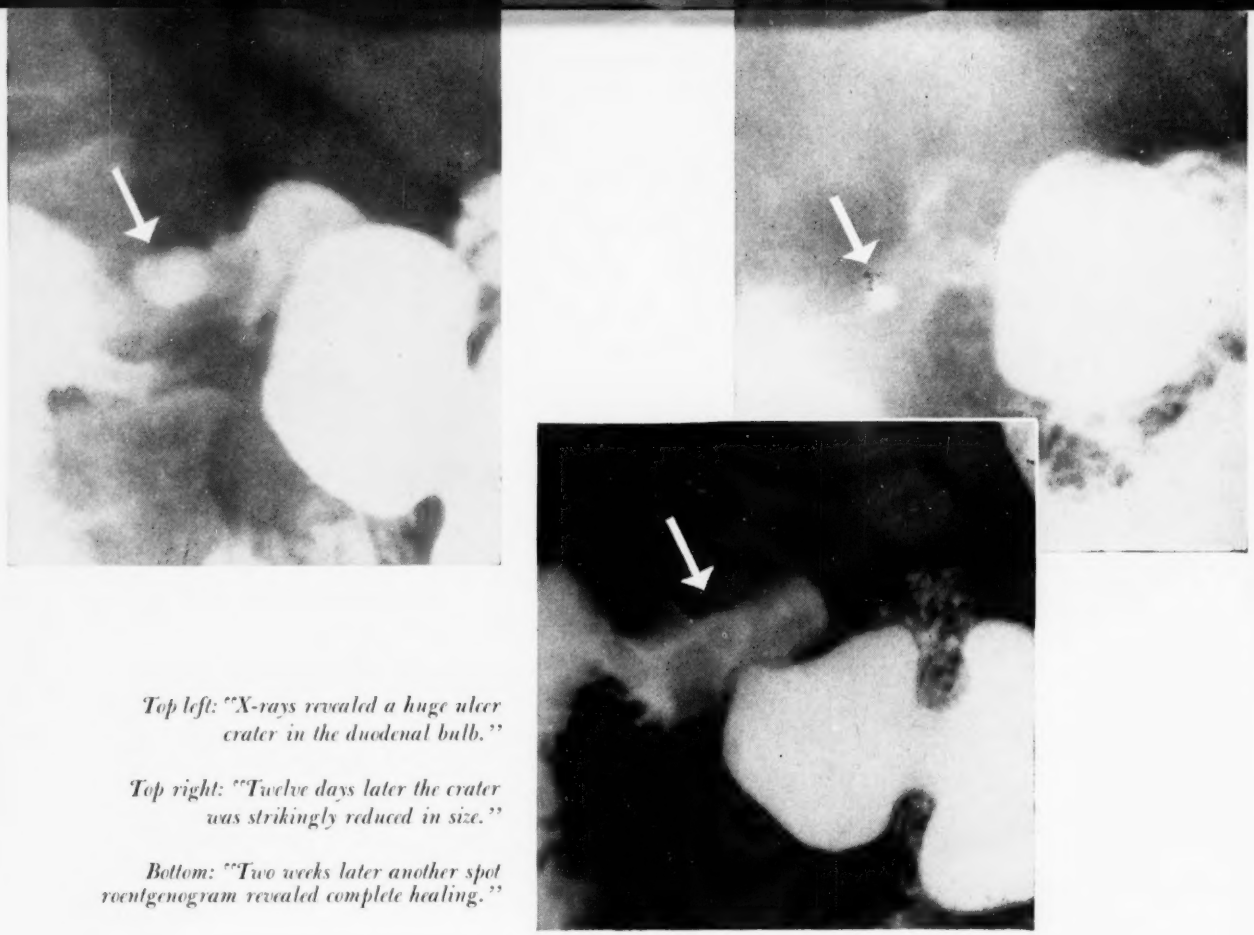

Top left: "X-rays revealed a huge ulcer crater in the duodenal bulb."

Top right: "Twelve days later the crater was strikingly reduced in size."

Bottom: "Two weeks later another spot roentgenogram revealed complete healing."

Rapid Healing of Duodenal Ulcer with Pro-Banthine®

CASE REPORT

J. L., male, age 39, refused surgery even though roentgen study revealed a huge ulcer crater in the duodenal bulb (top left). He was placed on a Pro-Banthine regimen of 30 mg. four times a day. After twelve days of therapy the crater was strikingly reduced in size (top right).

Two weeks later another spot roentgenogram revealed complete healing (bottom). "This ulcer crater was unusually large, yet on 30 mg. of Pro-Banthine [q.i.d.] the patient's symptoms were relieved in forty-eight hours and a most dramatic diminution in the size of the crater was evident within twelve days."

Schwartz, I. R.; Lehman, E.; Ostrove, R., and Seibel, J. M.: A Clinical Evaluation of a New Anticholinergic Drug, Pro-Banthine, to be published.

Pro-Banthine (brand of propantheline bromide) is a new and improved anticholinergic agent with minimal or no side reactions.

Pro-Banthine inhibits neural impulses at both the sympathetic and parasympathetic ganglia and at the postganglionic nerve endings of the parasympathetic system. It is valuable in many conditions in addition to peptic ulcer, notably gastritis, pancreatitis, intestinal hypermotility, genitourinary spasm and hyperhidrosis.

Pro-Banthine is available in three dosage forms: 15 mg. sugar-coated tablets; Pro-Banthine (15 mg.) with Phenobarbital (15 mg.), sugar-coated tablets, for use when anxiety and tension are complicating factors; ampuls of 30 mg. for more rapid effect and in instances when oral medication is impractical or impossible.

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